Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Clinical Evaluation Report
Prescription Medicines Authorisation Branch

Active substance:
Fixed-dose combination of:
- **lidocaine (lignocaine) hydrochloride,**
- **tetracaine (amethocaine) hydrochloride, and**
- **adrenaline (epinephrine) acid tartrate**

Product name:
LACERAINE® Gel Topical Wound Anaesthetic

Sponsor:
Phebra

Submission number:
OM-2022-00069-1

eSubmission number:
e006280

Clinical evaluator: Dr s22

Date of clinical evaluation report: 27 January 2023

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and Aged Care and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989*, applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

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List of abbreviations

Abbreviation	Meaning
AE	Adverse event
ALA	Adrenaline, lignocaine, amethocaine
AHFS	American Hospital Formulary Service
AR	Adverse reaction
CTD	Common Technical Document
DB	Double-blind
ED	Emergency department
FPS - R	Faces Pain Scale - Revised
IQR	Interquartile range
LA	Local anaesthetic
LAT	Lidocaine, adrenaline, tetracaine
LET	Lidocaine, epinephrine, tetracaine
LI	Local infiltration
MEGX	monoethylglycinexylidide
OTC	Over the counter
PD	Pharmacodynamic (s)
PK	Pharmacokinetic (s)
RCT	Randomised, controlled, trial
SB	Single-blind
SE	Standard error
SD	Standard deviation
TAC	Tetracaine, adrenaline, cocaine
VAS	Visual analogue (analog) scale
VAS - C	Visual analogue (analog) scale - colour

List of tables

1. Submission details

1.1. Identifying information

Submission number	OM-2021-GL-08608
eSubmission number	e006280
eSubmission sequences covered in this report	0000
Sponsor	Phebra
Trade name	Laceraine® Gel Topical Wound Application
Active substance	Fixed-dose combination of lidocaine (lignocaine) hydrochloride, tetracaine (amethocaine) hydrochloride, and adrenaline (epinephrine) acid tartrate

1.2. Submission type

This is an application (N5) from Phebra to register Laceraine® Gel Topical Wound Application, a new fixed-dose over the counter (OTC) medicine.

1.3. Drug class and therapeutic indication

1.3.1. Drug class

Laceraine is a fixed-dose combination of two local anaesthetics, lidocaine (lignocaine) hydrochloride and tetracaine (amethocaine) hydrochloride, combined with a vasoconstrictor adrenaline (epinephrine) acid tartrate.

1.3.2. Therapeutic indication

Laceraine Gel Topical Wound Anaesthetic is indicated for topical application to superficial wounds and lacerations to provide localised surface anaesthesia for wound closure. It may be used to provide topical anaesthetic relief for cleaning, irrigation and debridement of painful minor wounds.

1.4. Dosage forms and strengths

Laceraine gel is prepared for topical application. It is a clear, colourless to straw coloured, particle-free, non-greasy, uniform semi-liquid application of moderate viscosity and free-flowing properties. It is presented as 4 mL of gel in a 7 mL amber glass sealed vial with a flip off cap, ring pull metallic collar and siliconised rubber stopper. The pack size is 5 vials. The gel should be used in one patient on one occasion only.

The active components and strengths of the three components as stated in the Sponsor's covering letter supporting the submission are:

- Lidocaine (lignocaine) hydrochloride monohydrate 42.66 mg/mL equivalent to lidocaine hydrochloride 40 mg/ml (4% w/v)
- Tetracaine (amethocaine) hydrochloride 5.0 mg/mL (0.5% w/v)
- Adrenaline (epinephrine) acid tartrate 1.8 mg/mL (0.18% w/v)

1.5. Dosage and administration

Laceraine Gel Topical Wound Anaesthetic is for topical use on broken skin only. The pharmaceutical form is an ***application***, described in the dossier as a ***gel*** (sterile-semi-liquid). The gel must not be injected. As with any local anaesthetic agent, the smallest effective dose should be used.

- Children 1 to 3 years – 0.1 mL/kg to a maximum recommended dose of 2 mL
- Children over 3 years– 0.1 mL/kg to a maximum recommended dose of 3 mL
- Adults and adolescents – 0.5 mL per cm laceration to a maximum recommended dose of 3 mL.

Prior to wound repair, test sensation to confirm adequate anaesthesia.

Method of administration:

Remove the cap, metal collar and bung from the vial. Using a plastic syringe draw up the gel from the vial. After the wound has been lightly cleaned of surface debris and clotted blood, apply the recommended dose of gel to the wound and wound margins, either directly (from the syringe used to draw up the gel) or using a cotton-tipped applicator. Cover with an occlusive clear film dressing. Use of gauze or island wound dressings is not recommended. Leave the gel and dressing in situ for 20 to 30 minutes (to a maximum of 60 minutes to avoid prolonged contact and possible absorption). Remove the occlusive dressing and clean or irrigate the wound of residual gel. The duration of anaesthesia is 45 to 60 minutes following the removal of the gel. Avoid application to mucous membranes and wounds with end arteriolar supply (see section 4.4 of the PI Special Warnings and Precautions for Use). Laceraine Gel Topical Wound Anaesthetic contains no antimicrobial preservative. Use in one patient on one occasion only and discard any unused gel. Do not use if gel is discoloured or if the plastic cap is lifted or removed from the product.

1.6. Proposed changes to the product documentation

Not applicable. The Product Information (PI) has not been previously submitted for evaluation to the Therapeutic Goods Administration (TGA).

2. Background

2.1. Information on the condition being treated

Superficial skin wounds and lacerations are common presentations to hospital emergency departments (EDs), general practitioners, and nurse practitioner units. Management of paediatric lacerations focuses on minimising pain and distress in order to allow thorough cleaning, debridement and repair.

2.2. Current treatment options

Topical Laceraine gel is a commonly used local anaesthetic in EDs for repair of simple skin lacerations in children. Other treatment options for controlling pain when repairing, cleaning or debriding superficial skin wounds not requiring IM or IV sedation or general anaesthesia include infiltration of local anaesthetic agents (i.e., lidocaine) with or without adrenaline. Other options include application of topical lidocaine combined with prilocaine preparations (EMLA), although this is not an approved indication for repair of lacerations. Topical anaesthetics for acute pain management are summarised in the Australian *Therapeutic Guidelines* (01/09/2021) (see Attachment 2, Section 13.2, pages 98-101).

2.3. Clinical rationale

Topical Laceraine gel is widely used in Australian hospitals to minimise pain and distress in paediatric patients undergoing superficial wound cleaning and wound closure.

2.4. Formulation

2.4.1. Formulation development

The Sponsor's covering letter stated that Phebra was approached in s.47 [redacted] Phebra developed a sterile solution containing the LAT combination based on a sterile gel product produced by Torbay Pharmacy, South Devon Health Care, NHS Trust, United Kingdom (UK). The Torbay product (since reformulated to a gel, known as "LAT Sterile Gel") has been compounded and supplied to UK hospital pharmacies since 1995 and remains available on Torbay's current product listing (as an unapproved medicine). A similar LAT solution, Topicaine®, has been available as a commercial registered product in New Zealand. This product has been evaluated by Medsafe and consent for supply was granted on 21 December 2006.

s.47 [redacted], Phebra has manufactured and supplied a topical LAT solution, similar to the Torbay Pharmacy product, s.47 [redacted] articularly in relation to its viscosity. The liquid solution supplied at the time required the use of cotton balls or swabs for application and retention over the wound. Depending on the location of the wound, and the age or compliance of the child, it was reported that it was often difficult to retain the soaked dressing in place or to contain runoff. Therefore, a formulation that avoided the need to use Laceraine soaked cotton wool dressings was regarded as ideal.

Accordingly, Phebra developed a viscous ***application,*** known as Laceraine® Gel Topical Wound Anaesthetic, with the same active ingredients at the same concentrations as the liquid formulation. The new formulation is a semi-liquid and therefore the dose form is an application. However, Phebra propose to use the term "gel" in the product name. s.47 [redacted]

The quantitative active ingredients of Laceraine gel are presented below in Table 1.

Table 1: Laceraine gel – Active ingredients.

Active Ingredient	Quantity (mg/mL)	Overage (%)	Function	Reference to Standard
Lidocaine (lignocaine) hydrochloride monohydrate	42.66*	0	Active	BP
Tetracaine (Amethocaine) hydrochloride	5.0	3	Active	BP
Adrenaline acid tartrate	1.8	10	Active	BP

*Equivalent to 40 mg/mL lidocaine hydrochloride.

Source: Module 3.2.P.1.2, Table 1.

2.4.2. Excipients

The excipients in Laceraine gel are summarised below in Table 2.

Table 2: Laceraine gel – Excipients

Excipient Ingredients	Quantity (mg/mL)	Overage (%)	Function	Reference to Standard
Sodium metabisulfite	s.47			
s.47				
Water for injections in Bulk (WFI)	s.47			
s.47				

Source: Module 3.2.P.1.2, Table 1.

2.5. Regulatory history

2.5.1. Australian regulatory history

As described above, LAT solution has been supplied in Australia by Phebra since at s.47 initially as a solution and subsequently as a gel. s.47

Phebra now propose to register Laceraine® Gel Topical Wound Anaesthetic. The registration dossier has been submitted to the TGA for evaluation via the over-the-counter (OTC) application route as an N5 level application (i.e., new OTC medicines that are not generics). The Sponsor states that a similar fixed combination medicine to Laceraine Gel Topical Wound Anaesthetic with the same actives (Topicaine) has been on the Medsafe New Zealand register from 2006. This satisfies the TGA's Literature Based Submission (LBS) requirement for established marketing history in an overseas country with comparable regulatory standards.

The three active ingredients of LAT (lidocaine, adrenaline and tetracaine are all on the Australian Register of Therapeutic Goods (ARTG). The proposed use of lidocaine in the combination is within the approved indications, dose range and routes of administration for this product. Adrenaline is approved for several indications and over a broad range of doses. In Australia, tetracaine is approved for intra-optic/ophthalmic use as an eye drop in strengths

0.5% (5 mg/mL) and 1.0% (10 mg/mL). However, internationally tetracaine is reported by the Sponsor to be used as a topical local anaesthetic in other settings (e.g., the nose and throat, 2%) as well as parenterally (e.g., 1% spinal anaesthesia: American Hospital Formulary Service [AHFS]). The AHFS also specifically recommends the use of tetracaine in combination with adrenaline (1%) to reduce the possibility of systemic absorption. Products combining tetracaine and lignocaine in creams and patches for topical anaesthesia are also stated by the Sponsor to be approved in international markets. Therefore, although the use of tetracaine in the proposed combination will constitute administration via a new route of administration (topically) in Australia, the Sponsor notes that the combination has been widely used, and has been evaluated by other regulatory authorities for that route of administration, including Medsafe, New Zealand.

In support of its application to register Laceraine® Gel Topical Wound Anaesthetic for the proposed therapeutic indications, the Sponsor provided a detailed justification for the proposed fixed-dose combination (Module 1.5.6 of the Dossier). The fixed combination has been justified by the Sponsor based on the European Union (EU) Guideline: *Guideline on clinical development of fixed combination medicinal products* (EMA/CHMP/158268/2017, 23 March 2017) which replaced: Fixed Combination Medicinal Products (CPMP/EWP/240/95 Rev 1, 2009), the older guidelines providing valuable explanatory rationale.

It is noted that the *EU Guideline on clinical development of fixed combination medicinal products* (EMA/CHMP/158268/2017, 23 March 2017) does not appear to have been adopted by the TGA. However, the TGA has adopted the EU *Guideline on clinical development of fixed combination medicinal products* (EMA/CHMP/240/95 Rev 1, 19 February 2009). The Sponsor's submitted justification document has been examined and is considered to have satisfactorily addressed the requirements of this document (see Section 6 of this CER).

2.5.2. Related submissions

The Sponsor has lodged an Australian Approved Name (AAN) application to the TGA seeking approval for the use of Adrenaline (epinephrine) acid tartrate to be used as one of the active ingredients of the OTC formulation, Laceraine® Gel Topical Wound Anaesthetic (AAN submitted on 20 September 2021).

2.5.3. Overseas regulatory history

Section 1.11.1 (Foreign Regulatory Status) states that "[n]o submission for Laceraine Gel Topical Wound Anaesthetic has been submitted to any other regulatory agency internationally". No reference in Section 1.11.1 has been made to Laceraine Gel Topical Wound Anaesthetic being "registered" in any country, although solution and/or gel formulations have been extensively used in Australia and the UK.

In other sections of the submission, the Sponsor states that a topical solution called Topicaine containing the same active ingredients as Laceraine Gel Topical Wound Anaesthetic has been approved by Medsafe and has been available in New Zealand since 2006. The submission included a copy of the New Zealand Data Sheet for Topicaine dated 25/06/2018 and located in the References for Module 5. The data sheet indicates that "Topicaine is intended for use in adults and children older than 1 year, as a topical anaesthetic for pain management when repairing wounds, particularly facial or scalp wounds. Its key feature is avoidance of the anaesthetic needle, which can be particularly traumatic for children and some adults with laceration injuries." The active products in Topicaine topical solution given in the NZ data sheet are: adrenaline acid tartrate 0.18% w/v, lidocaine hydrochloride 4% w/v, and tetracaine hydrochloride 0.5% w/v. This formulation is the same as that for Laceraine Gel Topical Wound Anaesthetic being proposed for Australian registration. The excipients in Topicaine topical solution include sodium metabisulfite 0.5% w/v as antioxidant and water for injection. The usual dose recommended in the NZ data sheet is approximately 0.1 mL/kg.

2.6. Guidance

s.47 [redacted]

Detailed information was provided by the Sponsor in Module 1 outlining the search strategy for clinical studies and nonclinical studies relevant to the LAT formulation being proposed for approval. The initial search for clinical publications relevant to the efficacy and safety of topical LAT solutions for the proposed usage appears to have been conducted by the Sponsor in June 2021. During the screening phase of the submission, Phebra received feedback from the TGA Librarian in relation to the clinical literature search strategy. Following communication between the TGA and the research librarian, who conducted the initial literature searches for the Sponsor, the clinical search strategy for LAT was updated. This involved conducting a bridging search to cover the period from June 2021 to 6 May 2022. Following this process, only one additional published article was identified as having relevance to the clinical efficacy and safety of Laceraine Gel (i.e., *Siembieda 2022,* a randomised single-blind study comparing triple applications of a LAT gel 10 minutes apart with a single application of a LAT gel for 30 minutes). In addition, one clinical study was identified in the bridging literature search which provided serum pharmacokinetic (PK) data for lidocaine and its major metabolite (monoethylglycinexylidide [MEGX]) following administration of 5 local anaesthetic formulations containing lidocaine to the intact skin of healthy volunteers (*Oni 2012*). This study was included in the submission as a supportive study.

2.7. Evaluator's commentary on the background information

The background information provided by the Sponsor is acceptable.

3. Contents of the clinical dossier

3.1. Overview

The Sponsor stated that the application is supported by a full Module 3 (quality) dossier and a Module 5 (clinical) dossier consisting of published studies identified by a systematic literature search performed in accordance with the TGA's literature-based submission (LBS) guidelines. The submission does not include any Module 4 (nonclinical) data as each of the three active ingredients has been previously evaluated by the TGA and is included either individually or in combination with other products on the ARTG. No company sponsored clinical studies with Laceraine gel (or Laceraine solution) have been performed.

3.2. Scope of the clinical dossier

3.2.1. Module 5

Module 5 included 14 published studies supporting the application to register Laceraine Gel Topical Wound Anaesthetic. The 13 clinical studies in patients have all been fully evaluated and key data from these studies have been included in the body of the CER and synopses of each of these studies have been provided in Section 12.1 of this CER. The pharmacokinetic study in healthy volunteers has been reviewed in Section 4 of this CER.

The 14 submitted studies were:

- Three (3) randomised controlled clinical trials comparing LAT solution with the active comparator TAC: Schilling 1995, Ernst 1995 and Ernst 1995b.
- Three (3) randomised controlled clinical trials comparing LAT solution with a placebo: Adler 1998, Harman 2013 and Priestley 2003.
- One (1) randomised controlled clinical trial comparing LAT solution with LAT gel: Resch 1998.
- Two (2) uncontrolled observational studies in patients receiving LAT but requiring additional anaesthesia: Vandamme 2015 and White 2004.
- Three (3) controlled clinical studies comparing LAT with injectable local anaesthetic: O'Connor 2010, Ernst 1997 and Lee 2013.
- One (1) randomised clinical study comparing triple administration of LAT with single administration LAT: Siembieda et al 2022.
- One (1) clinical study in healthy volunteers examining the pharmacokinetics (PK) of lidocaine and its active metabolite, monoethylglycinexylidide (MEGX) following administration of 5 topical anaesthetics including LAT gel: Oni 2012.

Module 5 also included a copy of the Cochrane Review *Topical anaesthetics for pain control during repair of dermal laceration* (Tayeb 2017). Relevant information from this study has been referred to in the body of this CER.

Module 5 also included a number of literature references. Information from three of these references has been specifically referred to in this CER: (1) The Sydney Children's Hospital Network *Laceraine wound application anaesthetic application – ED: procedure*, effective date 01/01/2021; (2) Therapeutic Guideline (Australia) *Topical local anaesthetics for acute pain management*, 01/09/2021; and (3) New Zealand Data Sheet for Topicaine, Topical solution, update of 25/06/2018.

3.2.2. Module 2

Module 2 included the following data: Common Technical Document (CTD) Introduction; Quality Overall Summary (QOS); Nonclinical Overview; Nonclinical Overview – Addendum; Clinical Overview; Summary of Clinical Efficacy; Clinical Overview Addendum; Summary of Clinical Safety; Synopses of Clinical Studies; Synopses of Individual Studies – Addendum Literature references.

3.2.3. Module 1

Module 1 included the following data: Sponsor's covering letter; life-cycle management tracking table; application form; Sponsor's response to TGA request for information in the screening phase; Product Information (PI), clean and justified; Consumer Medical Information (CMI), clean: clean mock-up labels for the carton and vials; information (CVs) on local (Australian) experts, Quality and Clinical; search strategies for identification of clinical and nonclinical published studies for inclusion in the literature based submission (LBS); Sponsor's justification document for the fixed-dose combination proposed for registration (i.e., topical LAT gel); master files; details of compliance with pre-submission consultations between the Sponsor and the TGA; and foreign regulatory status for topical LAT gel.

3.3. Paediatric data

The majority of the 13 clinical studies in patients were conducted in paediatric populations. Studies exclusively in paediatric populations accounted for 78.6% (820/1043) of evaluable subjects receiving a LAT combination product (Priestley 2003, Schilling 1995, Harman 2013,

Resch 1998, O'Connor 2010, Ernst 1995b, White 2004, and Siembieda 2022). Clinical studies exclusively in adults accounted for 48 evaluable patients receiving a LAT combination product (Ernst 1995), and studies with a mixed population of children and adults accounted for 175 evaluable patients (Adler 1998, Vandamme 2015, Ernst 1997 and Lee 2013).

Comment:

The total number of subjects in the 13 clinical trials in patients is calculated by the evaluator as 1043. See discussion about subject numbers in the submission in Section 8.1 of this CER.

3.4. Good clinical practice

Of the 13 published clinical studies included in the submission, reference was made to informed consent and or local ethic committee approval in 12 of the studies. The only exception was *O'Connor 2010*, which was a retrospective review of patient emergency department (ED) records undertaken in an Irish hospital to assess whether the introduction of LAT gel in the ED helped to reduce the number of specialist referrals.

3.5. Evaluator's commentary on the clinical dossier

The Sponsor's LBS clinical dossier allowed for a meaningful clinical evaluation to be made of the efficacy and safety data of Laceraine Gel Topical Wound Anaesthetic for the proposed usage. In the submitted data, abbreviations for the lidocaine (lignocaine), adrenaline (epinephrine), and tetracaine (amethocaine) formulations were LAT, LET and ALA. In the body of the report, the abbreviation LAT has been predominantly used, and in the synopses the abbreviations used in the published reports have been maintained. Of note, in each of the Sponsor's clinical summary documents located in Module 2, the published study *Adler 1998* has been consistently misspelt as "*Alder 1998*".

4. Pharmacokinetics

4.1. Overview

The submission included only one pharmacokinetic (PK) study relating to the topical application of LAT gel to intact skin in healthy volunteers (Oni 2012). The Sponsor submitted *Oni 2012* as a supportive study, but the study appears to have limited relevance as regards the purpose of the submission. The study is reviewed below in Section 4.2. There were no PK studies relating to LAT formulations solutions in patients when applied to lacerations for anaesthesia prior to or during suturing.

The Sponsor's *Justification for a Fixed-Dose Combination (Module 1.5.6)* provided a brief summary of the PK of lidocaine, tetracaine, and adrenaline. The three components of the proposed LAT gel formulation have the potential to cause systemic toxicity when applied topically to open wounds. However, no clinically significant systemic adverse reactions associated with topical LAT formulations for the repair of lacerations were reported in the 13 clinical studies submitted by the Sponsor and the Cochrane Review of *Topical anaesthetics for pain control during repair of dermal laceration* (Tayeb 2017). It is considered that the absence of PK data following administration of topical LAT gel for the proposed indication should not preclude registration of the product.

4.2. Oni 2012

The submission included one PK study in healthy volunteers undertaken in Texas, USA (Oni 2012). The study was a prospective, randomised, parallel-group clinical trial of 5 topical anaesthetics containing lidocaine designed to compare the serum concentrations of lidocaine and monoethylglycinexylidide (MEGX), an active metabolite of lidocaine, following administration of the products to the intact skin of the face and neck. The study included 25 healthy volunteers of both sexes (17 women, 8 men) of mean age 26 years (range: 22-62 years).

Five of the 25 subjects were randomly allocated to each of the 5 topical lidocaine products. After a patch test for adverse reactions, a single administration of 30 g of the assigned topical anaesthetic was applied to the face and neck and covered with an occlusive dressing for 60 minutes. Blood was drawn at 90, 120, 150, 240, and 480 minutes to measure serum concentrations of lidocaine and MEGX. The 5 topical lidocaine products were:

- Group A: 30 g Topicaine (active ingredient 4% lidocaine)
- Group B: 30 g eutectic mixture of 2.5% lidocaine, 2.5% prilocaine (generic form of EMLA)
- Group C: 30 g LMX-4 (active ingredient 4% lidocaine)
- **Group D: 30 g LAT (4% lidocaine, 1:2000 epinephrine, and 0.5% tetracaine)**
- Group E: 30 g BLT (20% benzocaine, 6% lidocaine, and 4% tetracaine)

Topicaine had the greatest absorbed serum levels of lidocaine (0.808 μg/mL) for an individual participant, followed by generic EMLA (0.72 μg/mL), LMX-4 (0.44 μg/mL), BLT (0.17 μg/mL), and LAT (0.13 μg/mL). Following topical application, on average, Topicaine had the highest serum lidocaine and MEGX levels (0.438 μg/mL and 0.0678 μg/mL, respectively). There were significant differences across the time-points between the serum levels of lidocaine (p=0.0002) and MEGX (p=0 .0045) in all five groups. LAT, the topical anaesthetic of interest, had the least absorption of all 5 study drugs, with 4 of the 5 patients in this group having no detectable serum levels of lidocaine or MEGX.

Two participants developed minor adverse reactions of erythema within the first four hours, with scaling and prolonged erythema at 48 hours, one in the Topicaine (4% lidocaine) group and one in the EMLA (2.5% lidocaine) group. All skin reactions resolved within seven days. One subject in the Topicaine group developed a more severe skin reaction that resulted in post-inflammatory hyperpigmentation over the cheeks and dorsum of the nose. This resolved with conservative care.

Comment:

The Sponsor comments that the dose of LAT used in this study (30 g) was approximately 10-times greater than the maximum 3 mL dose of Laceraine (3 g) for the proposed indication, and that the head and neck approximated 8% of the body surface area. Therefore, as 4 of the 5 patients in the LAT group had no detectable serum levels of lidocaine or MEGX, toxic effects of lidocaine following the proposed use of LAT gel for the proposed indications are unlikely. In *Oni 2012*, LAT gel was applied to intact skin while the intended use of LAT gel will be to broken skin. Therefore, it is possible that there might be some systemic absorption following application of LAT gel to lacerations. However, reassurance is provided by the small number of adverse events observed in approximately 1000 patients treated with LAT in the 13 studies submitted for evaluation. The authors of *Oni 2012* concluded that "topical anaesthetics are safe, but systemic absorption in some individuals can reach unpredictably high levels. OTC products were found to have the greatest level of systemic absorption and could persist in the bloodstream at 8 hours post-application. To avoid

adverse toxic effects topical anaesthetics should be used under the supervision of a healthcare professional".

5. Pharmacodynamics

There were no studies in the submission providing human pharmacodynamic (PD) data. However, effective anaesthesia of LAT gel and solution formulations observed in the 13 clinical studies submitted by the Sponsor can be considered to be a clinically relevant demonstration of the primary pharmacodynamics of the products (i.e., local anaesthesia). The Sponsor's *Justification for a Fixed-Dose Combination (Module 1.5.6)* provided a brief summary of the PD of lidocaine, tetracaine, and adrenaline. Overall, the pharmacodynamics of the three products found in the LAT gel formulation in humans are well understood.

6. Dosage selection for the pivotal studies

The Sponsor's provided a *Justification for a Fixed-Dose Combination* for topical LAT gel for the proposed usage in Module 1.5.6 of the submission. The fixed combination, consisting of 2 local anaesthetics and a vasoconstrictor, was justified by the Sponsor based on the EU document: *Guideline on clinical development of fixed combination medicinal products* (EMA/CHMP/158268/2017 23 March 2017) which replaced: *Guideline on clinical development of fixed combination medicinal products* (CPMP/EWP/240/95 Rev 1, 2009). The Sponsor commented that the older guidelines provided valuable explanatory rationale for fixed combination medicines.

I have read the Sponsor's justification document and agree with its conclusions supporting the fixed-dose topical LAT gel combination being proposed for registration. However, it is noted that the EU (2017) guideline for fixed combination medicinal products appears not to have been approved by the TGA, while the relevant EU (2009) guideline has been approved. The key features of the justification provided by the Sponsor for the fixed-dose combination are summarised below:

1. Valid therapeutic principles: The particular combination of the active substances proposed is based on valid therapeutic principles. The 2 local anaesthetics lidocaine and tetracaine provide effective topical anaesthesia with analgesia, while the vasoconstrictor adrenaline helps to localise the anaesthetic field and aids haemostasis. The formulation is well established at a ratio of lidocaine 4% to adrenaline 0.1% to tetracaine 0.5%. It is described and supported by reviews, hospital treatment guidelines and published randomised controlled trials (RCT) and a Cochrane review.

2. Potential advantages: The potential advantages of Laceraine relate to a simplification of therapy by combining 3 active ingredients into a gel. The separate individual active substances have proven efficacy and safety over decades. The amounts of each of the 3 active ingredients are all below the maximum doses (/kg) for local anaesthesia/vasoconstriction. The actual dose delivered is determined by the physician/nurse based on the patient's weight and extent of the laceration/injury being treated. Laceraine is supplied in vials containing 4 mL of gel, although practically the maximum extractable volume is 3 mL. The proposed dose in paediatric settings is 0.1 mL/kg with a maximum dose of 2 mL for patients < 3 years (approximate weight 12-18 kg). An absolute maximum recommended dose is 3 mL, which has consistently been shown to be sufficient in clinical trials of adolescent and adult subjects. Therefore, a single vial provides sufficient product for any single application and the presentation supports efficient dosing at recommended dose levels. In Australia, most emergency departments utilise electronic prescribing which requires all paediatric patients to

be weighed at triage and the weight and dose to be confirmed by the authorised prescriber. This mechanism ensures that maximum doses of products are not exceeded.

3. Potential disadvantages: While the theoretical disadvantage to any fixed combination product is that a full combination which meets the needs of the average patient is unlikely to be ideally adjusted for the needs of each individual patient, the quantity of each active substance has been determined based on well-established dosage guidelines to a suitable standard formulation. There are very few circumstances in which alternatives, should there be a desire to use only 1 or 2 of the active ingredients, would not also be available within an emergency or acute care setting.

4. Duration of action: Although the 2 anaesthetic ingredients have different onset of action, lidocaine being short-acting and tetracaine long-acting, the use of these 2 anaesthetic agents together allows a level of synergy, promoting rapid onset and effective duration of anaesthesia for the proposed setting. The adrenaline facilitates a local effect by vasoconstriction, reducing systemic absorption and providing a level of haemostasis.

5. Contribution of each ingredient to the combination: Each of the active ingredients contributes to the desired dual effect of anaesthesia (with analgesia) and vasoconstriction.

6. Adverse events: None of the active ingredients has been included in the proposed combination either to counteract adverse reactions to the other ingredient(s), or with the intention of producing unpleasant adverse effects as a means of preventing abuse (misuse) of the other ingredient(s).

7. Critical dose range or narrow therapeutic index: The active ingredients are present at doses which ensure, as far as possible, that no toxic level of any individual ingredient can be reached if one of more of the ingredients are absorbed from the site of application. None of the active ingredients has either a critical dose range or a narrow therapeutic index. The ratio of lidocaine 4% to adrenaline 0.1% to tetracaine 0.5% is supported by clinical reviews, guidelines and experience. The inclusion of the adrenaline, particularly supports safety through its action to cause vasoconstriction, thus reducing any systemic absorption of the anaesthetic ingredients which could (theoretically) lead to systemic toxicity. Dose is optimised on a patient-by-patient basis by effectively titrating the amount of product applied to the wound according to the size and complexity of the laceration. Anecdotal experience has revealed that a lower volume of Laceraine gel than of the Laceraine solution is required to achieve adequate and effective anaesthesia in children, as the gel remains in contact with the wound, whereas some of the solution is lost and/or wasted in the process of application. As a single vial contains the maximum recommended dose, the amount can be adjusted if a greater dose or duration of activity is required without concerns of critical dose or possible toxicity.

7. Clinical efficacy

7.1. Studies providing evaluable efficacy data

The submission included 13 published clinical studies supporting approval of LAT gel for the proposed indication. The Sponsor divided the 13 studies based on the concentration of the active agents in the LAT formulation used in the studies: 8 Primary Studies assessing lidocaine 4%, adrenaline 1:1000 (0.1%) and tetracaine 0.5%; and 5 Supportive Studies assessing lidocaine 4%, adrenaline 1:2000 (0.5%) and tetracaine 0.5%. However, in this evaluation the focus has been on grouping the 13 studies according to design, irrespective of the LAT formulation used in the studies.

Each of the 13 studies have been fully evaluated. The key features of the studies are discussed below in this section of the CER and synopses of each of the studies are provided in Section 12.1 of this CER. The studies are listed below:

- Three (3) randomised, active-controlled, double-blind studies comparing LAT with TAC (i.e., tetracaine 0.5%, adrenaline 1:2000 [0.05%] and cocaine 11.8%) for repair of lacerations: *Schilling 1995, Ernst 1995*, and *Ernst 1995b.*
- Three (3) randomised, placebo-controlled, double-blind studies comparing LAT with placebo for repair of lacerations: *Adler 1998, Priestly 2003,* and *Harman 2013*.
- One (1) randomised, active-controlled, single-blind study comparing LAT solution with LAT gel for repair of lacerations: *Resch 1998.*
- Two (2) uncontrolled case-series assessing patient requirement for additional anaesthesia following administration of LAT for repair of lacerations: *Vandamme 2015* and *White 2004*.
- Two (2) randomised, active-controlled, unblinded studies comparing LAT with infiltrated lidocaine for repair of lacerations: *Ernst 1997* and *Lee 2013*.
- One (1) retrospective case series assessing LAT gel for repair of lacerations with other topical anaesthetics used prior to the introduction of LAT gel: *O'Connor 2010.*
- One (1) randomised, interventional, single-blind study comparing single-dose LAT with triple-dose LAT for repair of lacerations: *Siembieda 2022*.

In addition to the 13 published clinical studies in patients referred to above, the submission also included relevant efficacy information from a Cochrane Review of *Topical anaesthetics for pain control during repair of dermal laceration* (Tayeb 2017), a guideline on the use of Laceraine for topical anaesthesia in the ED prepared by The Sydney Children's Hospital Network (2021) (see Attachment 1, Table 13.1, pages 91-97, and an extract from the Australian Therapeutic Guidelines (2021) relating to *Topical local anaesthetics for acute pain management* (see Attachment 2, Table 13.2, pages 98-101)

The totality of the efficacy data allowed for adequate clinical evaluation of the efficacy and safety of Laceraine Gel for the proposed usage.

7.2. LAT vs TAC – randomised, active-controlled, double-blind studies

The submission included three, prospective, randomised, controlled, double-blind clinical trials comparing LAT with TAC for topical anaesthesia for suturing uncomplicated lacerations of the face and scalp (Schilling 1995, Ernst 1995, and Ernst 1995b). In each of the three studies, the double-blind, active control was topical TAC (tetracaine 0.5%, adrenaline 0.5%, and cocaine 11.8%) designed to match the physical appearance of the LAT solution or gel used in the studies.

In *Schilling 1995*, the LAT solution comprised lidocaine 4%, adrenaline 0.1%, and tetracaine 0.5%, and was applied as a 3 mL dose for 15 minutes. In *Ernst 1995*, the LAT solution comprised lidocaine 4%, adrenaline 0.05%, and tetracaine 0.5%, and was applied as a 3 mL dose for a minimum of 10 minutes to a maximum of 30 minutes. In *Ernst 1995b*, the LAT gel comprised lidocaine 4%, adrenaline 0.05%, and tetracaine 0.5% supplied in 3 mL syringes and applied using a cotton-tipped applicator for a minimum of 10 minutes to a maximum of 30 minutes

- ***Schilling 1995 (USA)***

Schilling 1995, was a randomised, active-controlled, double-blind study designed to compare the duration of anaesthesia experienced with LAT solution with TAC solution during suturing of uncomplicated lacerations on the face or scalp in children. In this study, 151 children and adolescents aged 1 to 17 years and median age of 6 years with uncomplicated lacerations of the

face (69.6%) or scalp (30.4%) received topical local anaesthesia with solutions of either TAC (n=73) or LAT (n=78). In this study, lacerations requiring repair were approximately 5x5 cm.

In the TAC and LAT groups combined, 116 of the 151 patients (76.8%) received adequate anaesthesia before suturing (i.e., no painful response as assessed by probing the wound margin with a 27-gauge needle). There was no difference between TAC (79.5%) and LAT (74.4%) when the proportion of those who had adequate anaesthesia were compared (χ^2, p=0.46).

Duration of anaesthesia during suturing was assessed in 115 of the 116 patients who had adequate anaesthesia. There was no difference in the mean total time the solution was effective in both the TAC (n=58) and LAT (n=57) groups (18.7 vs 18.0 minutes respectively, p=0.71).

In this study, complete anaesthesia was defined as suturing that finished without supplemental lidocaine or a painful response requiring supplemental lidocaine at least 30 minutes after removal of the anaesthetic solution from the wound, partial anaesthesia was defined as painful response requiring supplemental lidocaine between 15 and 30 minutes after removal of the anaesthetic solution from the wound, and incomplete anaesthesia was defined as painful response requiring supplemental lidocaine within 15 minutes after removal of the anaesthetic solution from the wound.

There was no difference between the TAC and LAT groups when the proportion of patients defined as achieving complete, partial, or incomplete were compared (χ^2, p=0.18). Physician rated complete anaesthesia during suturing was achieved by 75.9% of patients in the TAC group and 82.4% of patients in the LAT group, and partial anaesthesia was achieved by 15.5% and 5.3% of patients in the two groups, respectively.

Most lacerations occurred on the forehead or eyebrow (49.3%), whereas lacerations on the scalp accounted for 30.4% of all lacerations, and lacerations on the cheek or chin accounted for 20.2% of all lacerations. There was no difference between TAC and LAT in adequacy of anaesthesia before suturing or duration of anaesthesia during suturing of lesions located on the forehead/eyebrow or scalp area. A statistically significant difference was identified between TAC and LAT in the duration of anaesthesia experienced during suturing of lacerations on the cheek or chin area (χ^2, p=0.04). [The numerical difference between the two groups in the duration of anaesthesia experienced during suturing of lacerations on the cheek or chin area could not be identified in the report].

In children aged < 6 years there was no significant difference between TAC and LAT in either adequacy of anaesthesia before suturing or the duration of anaesthesia during suturing. In children aged ≥ 6 years, there was no significant difference between the two groups in the adequacy of the anaesthesia before suturing, but there was a significant difference between the two groups in the duration of anaesthesia during suturing favouring TAC over LAT (χ^2**,** p=0.01). In patients aged ≥ 6years there was a higher proportion of children experiencing complete or partial anaesthesia during suturing in the TAC group (100%) than in the LAT group (82%).

No adverse effects were noted after application of the anaesthetic solutions or during suturing in any patients during this study.

Comment:

The study showed no statistically significant or clinically meaningful differences between TAC and LAT solutions as regards the adequacy of topical anaesthesia prior to suturing or effectiveness during suturing in a population of children and adolescents with uncomplicated lacerations of the face or scalp.

- ***Ernst 1995 (USA)***

Ernst 1995, was a prospective, randomised, active-controlled, double-blind clinical trial designed to compare LAT solution with TAC solution for efficacy, adverse effects and costs when used for suturing linear lacerations of the face or scalp in adults. In this study, 95 adults with

uncomplicated linear lacerations of the face (n=81) or scalp (n=13) less than or equal to 7 cm in length were included in the statistical analysis (no location details were provided for 1 patient). Of the 95 patients included in the analysis, 48 received LAT solution and 47 received TAC solution. There was no significant difference between the two groups in mean length of laceration (2.6 cm, LAT vs 2.3 cm, TAC), the mean volume of local anaesthetic used (1.6 mL in both groups) or the median number of sutures placed (6 in both groups).

Patients reported the number of sutures causing pain, and patients and physicians rated the overall pain of suturing using a standard 10-cm linear visual analog scale (VAS), with 0 corresponding to no pain and 10 to worst possible pain.

According to patients, the percentage of sutures causing pain was statistically significantly lower for LAT than for TAC (median percentage of sutures causing pain 0 in both treatment groups; mean rank sum test 42.8 in the LAT group and 53.3 in the TAC group, p=0.036).

Physicians reported LAT to be significantly more effective than TAC in reducing pain (i.e., VAS median pain scores = 0 [range: 0 to 5] vs 1 [range: 0 to 6], respectively; mean ranked sum = 41.6 vs 54.6, respectively, p=0.0093).

However, patients did not report a significant difference between LAT and TAC as regards pain (i.e., VAS median pain scores = 0 [range: 0 to 4] vs 0 [range: 0 to 6], respectively; mean ranked sum = 45.3 vs 50.8, respectively, p=0.266).

Follow-up was accomplished in 91 of 95 patients (95%) with no reported complications for either medication.

Comment:

According to patients, the percentage of sutures causing pain was significantly lower in the LAT group than in the TAC group. As regards effectiveness of the two topical formulations for reducing pain during wound closure, physicians reported significantly greater effectiveness in the LAT group than in the TAC group, while no significant difference in effectiveness between the two groups was reported by patients. Overall, the data showed that LAT was at least as effective as TAC for local topical anaesthesia for the repair of uncomplicated linear lacerations (≤ 7 cm in length) of the face or scalp in adults.

- ***Ernst 1995b (USA)***

Ernst 1995b, was a prospective, randomised, active-controlled, double-blind clinical trial designed to compare LAT gel with TAC gel for efficacy, side-effects and costs when used for suturing linear lacerations of the face or scalp in children. In this study, 95 children and adolescents aged 5 to 17 years with uncomplicated linear lacerations of the face (n=64) or scalp (n=31) less than or equal to 7 cm in length were included in the statistical analysis. Of the 95 patients in the analysis, 48 received LAT gel and 47 received TAC gel. The median age of patients in the LAT group was 7 years (range: 5-16 years) and 8 years (range: 5-17 years) in the TAC group. There was no significant difference between the two groups in media length of laceration (2.0 cm in both groups), the mean volume of local anaesthetic used 1.5 mL in both groups) or the median number of sutures placed (5 in the LAT gel group and 4 in the TAC gel group.

According to patients/parents, there was no significant difference between the two treatment groups in the mean percentage of sutures causing pain (mean 18% [range: 0 to 100%, IQR = 0 to 25%] in the LAT gel group vs mean 13% [range: 0 to 100%, IQR = 0 to 20%] in the TAC gel group; mean ranked sum test = 49.57 vs 46.39, respectively, p=0.51).

Physicians and patients/parents separately rated the overall pain of suturing using a modified multi-dimensional scale for pain assessment specifically for children (rated from 0 corresponding to no pain to 10 corresponding to worse pain ever).

As assessed by physicians, the median pain score associated with suturing using the multi-dimensional pain scale was 2 (range: 0 to 7, IQR = 3.0 to 0.0) in both the LAT and TAC gel groups, with mean ranked sum scores of 48.7 and 47.3, respectively, p=0.80. As assessed by patients/parents, the median (range) pain scores associated with suturing using the multi-dimensional pain scale were 2 (range: 0 to 8, IQR = 5.0 to 0.0) in the LAT gel group and 2 (range: 0 to 7, IQR = 3.0 to 0.0) in the TAC gel group, with mean ranked sum scores of 49.0 and 46.9, respectively, p=0.71.

Follow-up was available in 85 of 95 patients. There was 1 wound infection in each of the TAC and LAT groups. No other problems or complications were reported in either the TAC or LAT groups.

Comment:

According to patients/parents, there was no significant difference between LAT gel and TAC gel as regards the percentage of sutures causing pain during wound repair. As assessed by both patients/parents and physicians, there was no significant difference in local anaesthetic effectiveness during wound repair between the two groups. Overall, the data showed that LAT was at least as effective as TAC for local topical anaesthesia for the repair of uncomplicated linear lacerations (≤ 7 cm in length) of the face or scalp in children and adolescents.

7.3. LAT vs placebo - randomised, controlled, double-blind studies

The submission included three prospective, randomised, controlled, double-blind clinical trials comparing LAT solution with placebo for topical anaesthesia for repair of uncomplicated superficial lacerations (Adler 1998, Harman 2013 and Priestley 2003).

In *Adler 1998*, the LAT solution of lidocaine 4%, adrenaline 1:1000 (0.1%), and tetracaine 0.5% was compared with the placebo solution of sterile water. The formulations were applied to the wound using a cotton ball saturated with 3 mL of either LAT or placebo. The solution was applied to the wound for a minimum of 20 minutes to a maximum of 30 minutes. Mild pressure was applied to the cotton ball by the patient's gloved hand throughout this period.

In *Priestley 2003*, the LAT solution of lidocaine 4%, adrenaline 1:1000 (0.1%), and tetracaine 0.5% was compared with the placebo formulation of adrenaline (1:1000 [0.1%]). Both solutions were presented in 3 mL containers.

In *Harman 2013*, the LAT gel of lidocaine 4%, adrenaline 1:1000 (0.1%), and tetracaine 0.5% was compared with the placebo gel formulation. Cotton balls soaked with 3 mL of study gel were applied to each wound. Study gel remained on the wounds for a minimum of 45 minutes to ensure effectiveness. Study gel was removed by treating physicians at the time of wound repair, not longer than 120 minutes after application. In this study, the wound was repaired by tissue adhesive rather than suturing.

- ***Adler 1998***

Adler 1998 (Canada) was a prospective, randomised, placebo-controlled (sterile water), double-blind clinical trial designed to assess the effectiveness of topical LAT solution for local anaesthesia for the repair of superficial lacerations. In this study, a convenience sample of 60 adult patients with uncomplicated, superficial lacerations ≤ 7 cm in length of the face (n=9), scalp (n=5), hand, arms, or legs (n=46) were randomised to LAT (n=30) or placebo (n=30). Patients with wounds older than 8 hours were excluded. The mean age of patients in the LAT group was 38 years compared with 41 years in the placebo group. The mean length of the laceration was 2.3 cm in the LAT group and 2.2 cm in the placebo group. The median number sutures placed in wounds in both treatment groups was 4, with a mean suturing time of 12.2 minutes in the LAT group and 13.1 minutes in the placebo group.

Pain scale values, as assessed by a standard 10-cm linear VAS (0 = no pain, 10 = worst possible pain) following probing of the wound margin with a 27-gauge needle, were statistically

significantly reduced in the LAT group compared with the placebo group (medians of 4.0 vs 5.0 cm, respectively; $p < 0.05$). Only 13 of the 30 patients (43.3%) in the LAT group required additional anaesthesia, while all 30 patients (100%) in the placebo group requested additional anaesthesia. The degree of pain following additional local anaesthetic was not statistically significantly different between groups (median pain scale values of 3.5 cm and 5.0 cm in the LAT and placebo groups, respectively, 0=0.09).

In the LAT group, median pain scores on needle probing of the wound were significantly lower in the face/scalp group than in the extremity group (0.5 cm vs 4.0 cm, respectively, $p < 0.05$). In the LAT group, injection of local anaesthetic was required in 1 of the 6 patients with a face/scalp laceration compared with 12 of the 24 patients with extremity lacerations. No significant differences were found between pain scale scores in different wound locations in the placebo group.

No adverse effects were noted after the application of either the LAT or placebo solution while the patients were in the ED. Telephone follow-up for 54 of the 60 patients occurred (2 patients in the LAT group and 4 patients in the placebo group could not be contacted). There was 1 report of a hand wound infection in the LAT group. No other problems or complications were reported in either of the two treatment groups.

Comment:

Pain scale values on needle probing were significantly reduced in the LAT group compared with the placebo group. Significantly fewer patients in the LAT group than in the placebo group required additional anaesthesia with an injectable anaesthetic to achieve adequate anaesthesia prior to suturing. The degree of pain following additional local anaesthetic was not significantly different between groups.

- ***Priestley 2003 (Australia)***

Priestley 2003 (Australia) was a prospective, randomised, placebo-controlled (adrenaline), double-blind clinical trial designed to determine whether application of topical LAT solution at triage reduces total treatment time for children with simple lacerations. The primary outcome measure was the total treatment time (defined as the difference between discharge time and triage time). The secondary outcomes were the proportion of children from each group who required sedation (an indicator of inadequate anaesthesia) and subgroup analysis by mode of wound closure.

In this study, 161 children with simple lacerations were eligible for analysis (LAT [n=84]; placebo [n=77]). The median age of children in both treatment groups was 4 years, and lacerations were predominantly of the head and face (n=135 [83.8%]). Patients with wounds > 6 hours were excluded. Sixty-five patients were sutured (n=27, LAT; n=38, placebo), 84 were treated with glue (n=51, LAT; n=33, placebo), 6 were treated with Steristrips (n=2, LAT; n=4, placebo), and 6 had no formal closure (n=3 in each group).

The median treatment time for the LAT group was 77 minutes compared with 108 minutes for the control group (effect size 31 minutes; 95% CI = 15 to 47 minutes; p=0.0019). There was an overall adjuvant sedation rate of 14.2% (23/161), with 10 (12%) patients in the LAT group and 13 (17%) patients in the placebo group requiring sedation (effect size 5%; 95% CI = –16% to 6%; p=0.46; χ^2). There were no observed complications relating to prolonged periods of LAT contact with wounds. Duration of application of LAT to wounds ranged from 20 to 125 minutes, with preservation of wound anaesthesia and no observed complications.

Comment:

The study showed that application of topical LAT at triage resulted in a significant reduction in total treatment time of approximately 30 minutes compared with placebo (adrenaline). There were no

assessments of either the adequacy of anaesthesia before suturing or effectiveness of anaesthesia during suturing.

- ***Harman 2013***

Harman 2013 (Canada) was a randomised, placebo-controlled (gel), double-blind, clinical trial designed to investigate whether pre-applied LAT gel would decrease pain in children during minor laceration repair using tissue adhesive. In this study, 203 children and adolescents with predominantly facial lacerations (n=192 [94.6%]) were included in the efficacy analysis, with 105 patients in the LAT gel group (mean age 5.1 years) and 98 patients in the placebo gel group (mean age 4.2 years). The inclusion criteria included wounds of < 3 cm in length. The mean lengths of the lacerations were similar in the two treatment groups (1.15 cm in the LAT group vs 1.31 cm in the placebo group), as was the mean age of the lacerations (1.93 hours in the LAT group vs 2.53 hours in the placebo group).

In this study, tissue adhesive rather than suturing was applied to repair the wound. Children receiving LAT gel reported less pain of application than children receiving placebo, based on 100 mm-unit colour VAS (median [IQR] values: 0.50 [0.25-1.50] for LAT vs 1.00 [0.38-2.50] for placebo; Wilcoxon rank-sum test p=0.01). However, the pre-defined minimally clinical significant difference of 10% on the VAS between groups was not reached.

When pain was reported using the Faces Pain Scale-Revised (FPS-R), children receiving LAT gel also reported less pain of application than those who received placebo (median [IQR]: 0.00 [0.00-2.00] for LAT vs 2.00 [0.00-4.00] for placebo; Wilcoxon rank-sum test p < 0.01). The difference in median scores in the FPS-R between the two groups was > 1, which the authors suggest represents a clinically significant difference in favour of the LAT group compared with the placebo group.

Pre-treatment with LAT significantly increased the proportion of pain-free procedures: 51.6% of children receiving LAT reported "no pain" according to the FPS-R compared with 28.3% of children receiving placebo (RR = 0.54 [95% CI: 0.37–0.80]). This difference remained significant after controlling for age (< 7 years vs ≥ 7 years) (RR = 0.55 [95% CI: 0.38–0.82]) and for level of physician training (RR=0.56 [95% CI: 0.38–0.84]).

Physicians more frequently rated wound haemostasis as complete in the LAT group (79 patients, 78.2%) than in the placebo group (54 patients, 59.3%) (p < 0.008).

No adverse effects were observed or reported when assessed by physicians in the ED or during telephone survey at 2 weeks' follow-up.

Comment:

The application of LAT gel prior to wound closure with tissue adhesive reduced pain compared with placebo gel. More than half of the patients (or their parents or guardians) who received LAT reported no pain during adhesive application, which was nearly double the proportion of pain-free procedures reported in the placebo group. In addition, physicians more frequently rated wound haemostasis as complete in the LAT group than in the placebo group.

7.4. LAT solution vs LAT gel

- ***Resch 1998***

Resch 1998 (USA) was the only prospective, randomised, single-blind, controlled clinical trial comparing LAT solution with LAT gel in a convenience sample of children with uncomplicated lacerations of the face or scalp. Both the LAT solution and LAT gel formulations used in this study comprised lidocaine 4%, adrenaline 1:1000 (0.1%), and tetracaine 0.5%.

In this study, 103 patients of mean age 5.6 years were randomised to LAT solution and 91 patients aged 5.8 years were randomised to LAT gel. Children were eligible if they had uncomplicated lacerations of the face or scalp that could be completely covered by a sterile 5x5-

cm gauze square. The mean length of the lacerations was 1.2 cm in the LAT solution group and 1.27 cm in the LAT gel group, and each of the LAT formulations remained on the lacerations for a mean of 21 minutes. The mean total number of sutures used to repair the lacerations was approximately 6 in both treatment groups, and the mean suture time in patients receiving adequate anaesthesia was 13 minutes in both treatment groups.

After patient enrolment, a nurse applied the randomised dose of study medication to the laceration for 20 minutes. In the LAT solution group, the solution was painted into the laceration with a cotton-tipped applicator. The remainder of the LAT solution was then applied to a 5x5 cm gauze pad that was held in place by the patient's guardian or secured with tape. In the LAT gel group, the gel was applied to the laceration with a cotton-tipped applicator and left uncovered.

Pain assessment was a 2-stage process that evaluated adequacy of anaesthesia before suturing (i.e., wound probing with 27-gauge needle) and effectiveness of anaesthesia during suturing (complete, partial or incomplete). In this study, pain was subjectively assessed before suturing as well as during suturing. In an attempt to limit interpersonal variability in pain assessment, the definition of a painful response was strictly defined before the study, and all suture personnel were instructed in the assessment of pain using this definition.

In this study, the adequacy of anaesthesia before suturing was similar for the LAT solution and the LAT gel formulations (84% [87/103] vs 82% [75/91]; difference 2% [95% CI: -8% to 13%]).

The effectiveness of anaesthesia was significantly different for the two formulations, largely because there were fewer patients with partial anaesthesia in the LAT gel group than in the LAT solution group (5% vs 21%, respectively, p=0.007 Fisher's exact test). Complete effectiveness was obtained in 85% (64/75) of patients in LAT gel group compared with 76% (66/87) of patients in the LAT solution group (difference = 9% [95% CI: –3% to 22%]), while the percentage of patients achieving incomplete anaesthesia was 9% (7/75) in the LAT gel group compared with 3% (3/87) in the LAT solution group (difference = –6% [95% CI: –2% to 14%). Of the 162 patients with adequate anaesthesia, data were available for all but 4 patients for the duration of anaesthesia. The mean duration of anaesthesia was the same in both groups (i.e., 21 minutes).

Comment:

The study demonstrated that both LAT gel and solution formulations provided similar anaesthesia before and during repair of uncomplicated lacerations of the face and scalp in children.

7.5. Uncontrolled studies with LAT – patients requiring additional anaesthesia

The submission included two uncontrolled studies assessing the need for additional anaesthesia in patients who received LAT for topical anaesthesia prior to repair of superficial lacerations (Vandamme 2015 and White 2004).

- ***Vandamme 2015***

Vandamme 2015 (Belgium) was a retrospective, observational study undertaken at the Ghent University Hospital, Belgium, as part of a quality audit. The aim of the study was to describe the potential value of the use of LAT gel in older children and adults with simple lacerations. In addition, the study aimed to define an adult population in which LAT gel could provide an advantage compared with infiltrative anaesthesia.

As part of the quality audit, data were extracted from all ED records for patients who had LAT gel applied for laceration repair in a 3-month period. In the 3-month study period, 275 patients older than 8 years of age were sutured in the ED. However, the study population for analysis (n=89) included only adult patients aged from 25 to 50 years, although the protocol specified that patients aged 8 years or older could be included. There was no discussion in the study report for the reasons why only adult patients were included in the analysis.

The LAT gel used at the hospital comprised lidocaine 4%, adrenaline 1:1000 (0.1%) and tetracaine 0.5%. The LAT gel was applied (at triage) at a dose of 0.5 mL/cm, up to a maximum of 1 mL/kg, directly into the wound and covered with an adherent dressing for 30 minutes. Of the 89 patients included in the analysis, 21 (23.6%) needed additional anaesthesia as assessed by 21-gauge needle probing of the wound following application of LAT gel prior to laceration repair (i.e., primary outcome measure). The median (IQR) pain score assessed by the VAS following needle probing was significantly higher in patients needing additional anaesthesia (2.0 [2.0, 4.0] cm) compared with patients not needing additional anaesthesia (1.0 [0.0, 3.0] cm); p=0.008. It was noted that only lacerations treated with sutures needed additional anaesthetic.

Lacerations on the head required significantly less additional anaesthesia than lacerations on the trunk, extremities, fingers or toes (i.e., 88.2% vs 69.1%; 95% CI for the difference between proportions = 1% to 34.8%; p < 0.05). There were significant differences in VAS scores at needle probing for the laceration sites: median (IQR) VAS values were 0 (0.0, 2.0) cm for head, 2.0 (0.5, 3.0) cm for extremities/trunk, and 3.0 (2.0, 4.0) cm for fingers/toes; Kruskal-Wallis test, p=0.001.

The length of lacerations was also associated with the need for additional anaesthetic (95% CI for the difference between medians = 0.5 to 2; p <0.005). Short lacerations required less additional anaesthetic compared with intermediate and long lacerations, and intermediate lacerations required less additional anaesthetic compared with long lacerations.

Although less lidocaine is absorbed topically from LAT gel, the study centre used the recognised maximum limit for injectable lidocaine and adrenaline as 7 mg/kg and therefore limited the use of LAT gel to 0.5 mL/cm laceration. No complications during the study were reported in the study population, although there was no follow-up.

Comment:

In this uncontrolled, retrospective, observational study in adults aged 25 to 50 years with simple lacerations on the head, extremities/trunk or fingers/toes anaesthetised with LAT gel prior to repair, 21 (23.6%) of 89 patients required additional anaesthesia. The median (IQR) pain score assessed by the VAS following needle probing was significantly higher in patients needing additional anaesthesia (2.0 [2.0, 4.0] cm) compared with patients not needing additional anaesthesia (1.0 [0.0, 3.0] cm); p=0.008. It was noted that only lacerations treated with sutures needed additional anaesthetic.

- ***White 2004***

White 2004 (USA) was a prospective, convenience sample, case series study designed to evaluate the effectiveness of LAT topical anaesthesia in children with simple finger lacerations ≤ 3 cm in length requiring repair, and to monitor any complications (i.e., the risk of digital ischaemia). The lacerations were equally distributed on the dorsal and ventral surfaces of the fingers.

All patients in this study had LAT gel applied to their wound, with a standardised maximum volume of 1.5 mL (0.5 mL/cm). An occlusive dressing was applied over the LAT gel to hold it in place for a 45-minute period. A total of 68 patients were enrolled in the study. One child was excluded from analysis because the laceration length was found to be > 3 cm, leaving 67 patients eligible for analysis. Of the 67 children included in the final analysis, the mean age was 11.9 years (range: 5-18 years). The LAT gel formulation used in this study was lidocaine 4%, adrenaline 1:2000 (0.05%) and tetracaine 0.5%, with methylcellulose and preservatives.

Adequacy of anaesthesia was assessed by probing with a 30-gauge needle after removal of LAT gel, followed by an examination of the digit for signs of ischaemia. The overall success rate for LAT gel on finger lacerations was 53.7% (95% CI: 41.1 to 66.0%; 36/67). As assessed by the VAS, mean discomfort of the procedure was 2.7 in LAT successes and 6.7 in LAT failures. There were no differences in success rates for age, sex, or race. No signs of digital ischaemia were noted in any of the 67 cases (0% [95% CI: 0.0% to 5.4%]).

In the LAT success group, 93.9% of parents and 94.3% of patients stated that they would use LAT again, while in the LAT failure group, 44.4% of parents and 50.0% of patients stated that they would use LAT again.

Ninety-three percent (62/67) of all patients enrolled were followed up with a phone call 3 to 5 days following laceration repair. There were no reported cases of ischaemia or infection.

Comment:

In general, it is advised that the use of local anaesthetics containing adrenaline for repair of digital lacerations be avoided because of the risk of ischaemia. However, in this study LAT gel appeared to be a safe and effective means of providing anaesthesia for the repair of simple finger lacerations in children. There were no reported cases of ischaemia or infection in the 67 children included in the study.

7.6. Topical LAT compared with injectable LA

Three (3) studies compared topical LAT with injectable local anaesthetic: Ernst 1997, Connor 2010, and Lee 2013.

- ***Ernst 1997***

Ernst 1997 (USA) was a prospective, randomised (unblinded), controlled intervention study comparing topical LAT gel with injectable buffered lidocaine/adrenaline as regards pain of application or injection, and effectiveness of anaesthesia for repair of simple linear lacerations 1.5 to 10 cm long. The majority of lacerations in both the topical LAT gel group and injectable lidocaine/adrenaline group were facial lacerations (17 vs 13, respectively), followed by extremity lacerations (13 vs 11, respectively) and scalp lacerations (3 and 7, respectively). The mean length of the lacerations was similar in both the topical LAT gel group and the injectable lidocaine/adrenaline group (2.3 cm vs 2.5 cm, respectively). The topical LAT gel formulation included lidocaine 4%, adrenaline 1:2000 (0.05%) and tetracaine 0.5%, supplied in 5 mL syringes.

The analysis population included 66 patients aged 5 years or older, with 33 being randomised to LAT gel (mean age 29 years) and 33 to injectable lidocaine/adrenaline (mean age 30 years). The analysis population included 13 children age 5 to 17 years. Two patients in the LAT group and no patients in the injectable buffered lidocaine/adrenaline group required further anaesthesia after initial treatment.

Physicians and patients ranked the pain of application, injection, and suturing according to a 10-cm VAS. Use of injection for local anaesthesia was found to be significantly more painful than application of gel when ranked by both physicians ($p < 0.001$) and patients ($p < 0.001$). For anaesthesia effectiveness during suturing, there was no difference according to patients ($p=0.48$) or physicians *(*$p=0.83$) between topical and injectable forms of local anaesthesia. The percent of sutures causing pain was numerically greater in the LAT group (13%) than in the injectable group (6%), but the difference between the groups was not statistically significant ($p=0.28$). Follow-up was available in 75% of the patients, with equal rates in the topical and injectable groups. No complications or wound infections were reported in either treatment group.

Comment:

LAT gel was significantly less painful to apply prior to suturing simple lacerations than injectable buffered lidocaine/adrenaline, and was comparable with injectable buffered lidocaine/adrenaline for local anaesthesia as regards effectiveness during suturing.

- ***O'Connor 2010***

O'Connor 2010 (Ireland) was retrospective review of patient ED records undertaken to assess whether the introduction of LAT gel helped to reduce the number of specialist referrals. A total of 397 children aged ≤ 14 years attended the ED with lacerations or incised wounds of ≤ 5 cm in length requiring suturing and were included in the study (201 patients pre-LAT group and 196 patients in the LAT group following the introduction of LAT). The mean±SD age of the children in both groups was similar (5.8±4 years, LAT and 6±3.5 years, pre-LAT).

The topical LAT gel formulation included lidocaine 4%, adrenaline 1:1000 (0.1%) and tetracaine 0.5%. The dose was 0.5 mL/cm, with a maximum dose of 2 mL for children < 3 years and 3 mL for children ≥ 3 mL.

Of the 196 patients in the LAT gel group, 19 (9.7%) were referred for speciality review compared with 39 (19.4%) in the pre-LAT group. Of these referred patients, general anaesthetic for wound repair was required for 15 (7.7%) patients in the LAT group compared with 31 (15.4%) patients in the pre-LAT group; p=0.018, Fisher's exact test.

The most common wound sites and ED treatments were comparable in both groups, with the face/forehead being the most frequent wound site (75 patients [37%] pre-LAT group and 70 patients [35.7%] LAT group). In both groups, the majority of patient referrals for repair were to maxillofacial surgeons (24 patients [11.9%] pre-LAT group and 10 patients (5.1%) LAT group).

Sixty-nine (34.3%) patients in the pre-LAT group and 69 (35%) patients in the LAT group were sutured, whereas 10 (5%) patients in the pre-LAT group and 12 (6%) patients in the LAT group received staples. No patients who received LAT gel required "top-up" infiltrative lidocaine analgesia.

Comment:

The introduction of topical anaesthetic gel in the ED significantly reduced the number of children with wounds referred to specialty teams for review or for repair under general anaesthesia. In this study, no reference was made to ethics committee approval and informed consent of the patients.

- ***Lee 2013***

Lee 2013 (Singapore) was a randomised, controlled, non-blinded study designed to compare LAT gel with conventional lidocaine 1% infiltration (LI) for repair of minor lacerations for comfort of application, efficacy, adverse effects and cost. The patient population comprised patients aged ≥ 1 year up to 70 years enrolled over a 4-month period. In this study, 23 patients were randomised to the LAT gel group and 17 patients were randomised to the LI group. The mean (SD) age was 36.8 (24.7) years in the LAT gel group and 46.2 (23.0) years in the LI group; there was only one patient aged < 10 years. The mean (SE) length of the wound was 3.1 (0.31) cm in the LAT gel group and 3.5 (0.36) cm in the LI group, and the mean (SE) depth of the wound was 0.5 (0.07) cm and 0.7 (0.08) cm, respectively. The majority of wounds were located on the head in both treatment groups (74%, LAT; 64.7% LI), with other wounds being located in the limbs in both groups.

The LAT gel formulation used in this study comprised lidocaine base 4%, racemic adrenaline 0.182% and tetracaine 0.569%. The doses used in the study for LAT gel or LI were not reported.

The pain of administering the anaesthetic was scored on a 10-cm VAS marked ranging from "most pain" to "no pain". Pain of administration was also scored in children aged ≤ 10 years by using the same scale but with faces drawn to describe facial expressions of pain (0 to 10).

The mean (SE) pain score prior to cleaning and suturing of minor lacerations was 2.5 (0.52) in 20 patients in the LAT gel group and 2.6 (0.58) in 16 patients in the LI group, p=0.87. The mean (SE) pain score during application of the anaesthetic was 1.5 (0.40) in the LAT gel group in 22 patients and 3.5 (0.46) in the LI group in 16 patients, p < 0.01.

Complications included wound infection (5 [20%] LAT vs 2 [14.3%] Li), wound dehiscence (1 [4%] LAT vs 0 LI), and loss of stitches (1 [4%] LAT vs 0, LI).

Comment:

The study demonstrated that LAT gel is as efficacious as lidocaine 1% infiltration for local anaesthesia prior to cleaning and suturing of minor lacerations.

7.7. Three applications vs One application of LAT gel

Siembieda 2022

Siembieda 2022 (USA) was a randomised, single-blind, controlled clinical trial designed to assess the anaesthetic effectiveness of single LAT gel for 30 minutes with triple LAT gel applied every 10 minutes for 30 minutes based on pain scores (VAS) immediately after the first suture was placed. In this study, the patient population children and adolescents aged 7 to 17 years with lacerations ≤ 3 cm in length. The LAT gel formulations in this study comprised lidocaine (4%), adrenaline (0.1%), and tetracaine (0.5%).

The study included 48 patients, 21 randomised to single LAT and 27 patients randomised to triple LAT. Overall, the mean (SD) age of the patients in the study was 10.5 (2.8) years, 81% were male, the mean (SD) laceration length was 1.7 (0.7) cm, and the site of the lacerations was predominantly the face/scalp (79%). There demographic data for the two treatment groups were reasonably well balanced.

The primary outcome was the difference in pain scores between single LAT and triple LAT immediately after the first suture was placed using a 100-mm VAS ranging from “no pain” to “pain as bad as it could possibly be”. The patient was asked to mark a pain rating along the scale with a pen. The pain rating was obtained by a nurse. The provider suturing the patient and the nurse obtaining the pain assessment were blinded to the study group.

The mean (SD) VAS score for single LAT patients was 16 (17), with a range of 0 to 48, and for triple LAT patients was 16 (24), with a range of 0 to 95; p=0.48, 2-sided Wilcoxon rank sum test. Pain scores did not differ significantly by patient sex or location of laceration, and there was no significant correlation between pain scores and age or the degree of blanching around the wound noted after LAT application.

Secondary outcomes in this study included the need for additional infiltrated local anaesthetic and provider and parent satisfaction. There was no significant difference between single LAT (4 of 21 patients [19%]) and triple LAT (5 of 27 patients [19%]) requiring additional anaesthesia. By treatment groups, 75% (15 of 20) of providers were very or extremely satisfied with single LAT versus 71% (17 of 24) with triple LAT, and 95% (20 of 21) of parents were very or extremely satisfied with single LAT versus 74% (20 of 27) with triple LAT.

Comment:

For children requiring suturing for repair of simple lacerations, there was no clinically meaningful difference in patients receiving one application of LAT gel for 30 minutes compared with three applications of gel applied every 10 minutes for 30 minutes. No information on adverse effects due to administration of LAT could be identified in the publication.

7.8. Other studies

The submission included a Cochrane Review of *Topical Anaesthetics for pain control during repair of dermal laceration* (Tayeb 2017). The objectives of this review were: (1) to assess whether benefits of non-invasive topical anaesthetic application occur at the expense of decreased analgesic efficacy; (2) to compare the efficacy of various single-component or multi-component topical anaesthetic agents for repair of dermal lacerations; and (3) to determine the clinical necessity for topical application of the ester anaesthetic, cocaine.

The review included randomised, controlled trials (RCTs) that evaluated the efficacy and safety of topical anaesthetics for repair of dermal laceration in adult and paediatric participants. The review included 25 RCTs involving 3278 participants. The small number of trials in each comparison group and the heterogeneity of outcome measures precluded quantitative analysis of data for all but one outcome: pain intensity.

The Authors of the review concluded that the "overall quality of the evidence according to the GRADE system is low owing to limitations in design and implementation, imprecision of results and high probability of publication bias (selective reporting of data). Additional well-designed RCTs with low risk of bias are necessary before definitive conclusions can be reached."

The GRADE system rates studies as high quality (further research is very unlikely to change confidence in the estimate of effect, moderate quality (further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate), low quality (further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate), and low quality (very uncertain about the estimate).

Of the 13 published clinical studies included in the Sponsor's submission, 4 studies were not included in the Cochrane Review: *Adler 1998* because the comparator was placebo rather than an active comparator; *Priestley 2003* because no outcomes of interest were measured (i.e., the primary outcome was treatment time rather than pain); *White 2004* as it was not a RCT and lacked a control group; and *Siembieda 2022* as it was published after the review.

Comment:

Despite the Cochrane Review's reservations, I consider that the clinical evaluation of the totality of the Sponsor's submitted data adequately support the efficacy of LAT gel for the proposed indication.

7.9. Evaluator's conclusions on clinical efficacy

1. Descriptive summary of relevant efficacy outcomes from the 13 clinical studies:

The submission included 13 studies providing satisfactory evidence of the efficacy of topical LAT for local anaesthesia for the repair of uncomplicated superficial lacerations of the skin in children, adolescents, and adults. The results from these 13 studies are summarised descriptively below:

- Three prospective, randomised, active-controlled, double-blind studies demonstrated the therapeutic equivalence of topical LAT compared with topical TAC for repair of superficial skin lacerations (Schilling 1995, Ernst 1995, and Ernst 1995b).
- Three prospective, randomised, placebo-controlled, double-blind studies demonstrated therapeutic superiority of topical LAT compared with placebo for repair of superficial skin lacerations (Adler 1998, Harman 2013 and Priestley 2003).
- One prospective, comparative, single-blind, intervention study demonstrated that LAT gel and LAT solution were similarly effective as topical anaesthesia for repair of uncomplicated lacerations of the face and scalp (Resch 1998).
- Two observational studies provided supportive evidence for the efficacy of LAT gel for the repair of superficial skin lacerations (Vandamme 2015, White 2004).
- Two prospective, randomised, controlled studies satisfactorily demonstrated the benefits of LAT compared with infiltrated local anaesthetic for repair of superficial skin lacerations (Ernst 1997, Lee 2012), as did one retrospective case series study (O'Connor 2010).

- One, randomised, interventional, single-blind study demonstrated similar anaesthetic efficacy for LAT gel administered as a single-application or as three applications for repair of simple lacerations requiring suturing (Siembieda 2022).

2. Patient population in the 13 studies:

The patient population in the 13 clinical studies included a total of 1043 evaluable patients comprising children, adolescents and adults treated with a LAT gel or solution. The treatment settings were confined to a single presentation to an ED. All studies identified the need for lacerations to be simple or superficial (i.e., could be repaired with single-layer closure). Lacerations with mucosal involvement were excluded, as were lacerations involving the nose, ear, genitalia, or underlying tissues (i.e., bone, cartilage, tendons, nerves). The length of the lacerations treated ranged from 0 to 10 cm, and the majority of studies (9 of 13) specified lacerations ≤ 7 cm. Two studies specified that wounds should ≤ 6 hours old (Priestley 2003 and Lee 2013), while five studies specified that wounds should be ≤ 8 hours old (Adler 1998, Ernst, 1995, Ernst 1995b, Ernst 1997, and White 2004).

The majority of studies were conducted in paediatric populations. Studies exclusively in paediatric populations accounted for 78.6% (820/1043) of evaluable subjects receiving a LAT combination product (Priestley 2003, Schilling 1995, Harman 2013, Resch 1998, O'Connor 2010, Ernst 1995b, White 2004, and Siembieda 2022). Studies exclusively in adults accounted for 48 evaluable patients receiving a LAT combination product (Ernst 1995), and studies with a mixed population of children and adults accounted for 175 evaluable patients (Adler 1998, Vandamme 2015, Ernst 1997 and Lee 2013). The majority of subjects receiving a LAT combination were males.

There were no studies specifically comparing the efficacy of a LAT combination between children and adults. One study compared TAC and LAT in paediatric patients aged < 6 years with paediatric patients aged ≥ 6 years for adequacy of anaesthesia before suturing and effectiveness of anaesthesia during suturing (Schilling 1995). There were no studies comparing the efficacy of LAT combinations in different racial groups.

The results of the 13 published clinical studies indicate that the application of topical LAT is an effective method of providing local anaesthesia for the repair of skin lacerations. The overall quality of the 13 studies is considered to be reasonable, given that the studies were carried out in the emergency departments of general hospitals or specialised children's hospitals.

The patient population described in the 13 published clinical studies is considered to be representative of Australian patients likely to receive Laceraine gel for repair of superficial dermal lacerations if the product is approved by the TGA. Therefore, the results of the clinical 13 clinical studies for the repair of uncomplicated skin lacerations can be reasonably extrapolated to the Australian population.

3. Treatment regimens:

Dosing of the LAT gel combination product used in the clinical studies was determined by the individual ED protocols in the clinical study sites. Therefore, as summarised below there were some differences between the dosing regimens used for the LAT gel formulations in different clinical studies:

- In *Resch 1998*, LAT gel was studied in 91 children (male:female = 70.6%:29.3%), with a mean age of approximately 6 years, and a mean laceration length of 1.27 cm. LAT gel (3 mL), comprising lidocaine 4%, adrenaline 0.1% and tetracaine 0.5%, was applied to the wound with a cotton tipped applicator and left uncovered for 20 minutes. The gel was irrigated from the wound with 20 mL of normal saline solution before suturing. Further irrigation of the wound with 100 mL of dilute povidone iodine was undertaken by the suturing personnel.

- In *Harman 2013*, LAT gel was studied in 105 children (male:female = 61.9%:38.1%), with a mean age of 5 years, and a mean laceration length of 1.27 cm. LAT gel (3 mL), comprising, lidocaine 4%, adrenaline 0.1% and tetracaine 0.5% was applied to the wound for a minimum of 45 minutes and not longer than 120 minutes.
- In *O'Connor 2010*, LAT gel was studied in 196 children (male:female = 68%:32%) aged ≤ 14 years with a mean age of 5.8 years and with a wound length requiring suturing of ≤ 5 cm. LAT gel, comprising lidocaine 4%, adrenaline 0.1% and tetracaine 0.5% was applied at a dose of 0.5 mL/cm up to 2 mL in children < 3 years and 3 mL in children ≥ 3 years. Half of the gel was applied directly onto the wound, and the other half was applied to non-absorbent gauze with an adherent dressing for 20 minutes. After this time, wound cleaning and suturing was to be completed within a further 20 minutes.
- In *Vandamme 2015*, LAT gel was analysed in 89 adult patients (male:female = 68%:32%) aged 20 to 50 years (narrative includes 89 patients but demographic data given for only 88 patients). The wound lengths in this study were categorised as short (0 to 2 cm), intermediate (2.1 to 4 cm), and long (4.1 to 7 cm). LAT gel comprised lidocaine 4%, adrenaline 0.1% and tetracaine 0.5%. LAT gel was applied at a dose of 0.5 mL/cm up to a maximum of 1 mL/kg directly into the wound using non-absorbent gauze and covered with an adherent dressing for 30 minutes. Additional anaesthesia with lidocaine injection was administered if anaesthesia was not adequate after this time.
- In *Ernst 1995b*, LAT gel was administered to 48 children (male:female = 79%:21%) aged 5 to 16 years with median age 7 years and a median wound length of 2 cm (range: 0.5 to 5 cm). LAT gel, comprising lidocaine 4%, adrenaline 0.05% and tetracaine 0.5%, was applied by cotton-tipped applicators into the wound and around the wound edges. The gel remained on the wound for a minimum of 10 minutes up to a maximum of 30 minutes. If anaesthesia was not adequate, then lidocaine 1% was injected.
- In *Ernst 1997*, LAT gel was administered to 33 subjects (male:female = 15%:85%) aged ≥ 5 years with a mean age of 29 years and a mean laceration length of 2.3 cm. LAT gel comprised lidocaine 4%, adrenaline 0.05% and tetracaine 0.5%. LAT gel administered at a total volume of 3 mL was applied with a cotton swab into the wound and up to l cm around the wound edge, and left in place for 10 minutes up to 30 minutes. If anaesthesia was not adequate, then lidocaine 1% was injected.
- In *Ernst 1995*, LAT gel was administered to 48 patients (male:female = 82%:18%) with a mean age of 33 years and a mean laceration length of 2.6 cm. LAT gel comprised lidocaine 4%, adrenaline 0.05% and tetracaine 0.5%. LAT gel available in 3 mL syringes was applied with small saturated pieces of cotton formed to fit into the wound and around the wound edges and mild pressure was applied. The gel remained on the wound for a minimum of 10 minutes to a maximum of 30 minutes. If anaesthesia was not adequate, then lidocaine 1% was injected.
- In *White 2004*, LAT gel was analysed in 67 patients (male:female = 66%:34%) aged 5 to 18 years with a mean age of 11.9 years and with a laceration length of ≤ 3 cm. LAT gel, comprising lidocaine 4%, adrenaline 0.05% and tetracaine 0.5%, was administered at a standardised maximum volume of 1.5 mL. Occlusive dressing was applied over the LAT gel to hold it in place for 45 minutes.
- In *Lee 2013*, the LAT gel group included 23 patients (male:female = 74%:26%) aged ≥ 1 to 70 years with mean age of 36.8 years and a mean laceration length of 3.1 cm. LAT gel comprised lidocaine 4%, adrenaline 0.05% and tetracaine 0.5%. LAT gel, available in pre-prepared 5 mL syringe, was squirted into and around the laceration with a syringe tip. The wound was then covered with a sterile piece of gauze and taped down with micropore. The gel was allowed to remain on the wound for 20 minutes.

- In *Siembieda 2022*, the LAT gel single-dose and triple-dose application groups included 21 (76% male) and 27 (85%) patients, respectively, aged from 7 to 17 years with lacerations ≤ 3 cm in length. LAT gel comprised lidocaine 4%, adrenaline 0.1% and tetracaine 0.5%. The single-dose group included one application 30 minutes before suturing and the triple-dose group included three applications 10 minutes apart before suturing.

4. Proposed LAT gel formulation:

The LAT gel formulation proposed for approval comprises the following active agents:

- Lidocaine (lignocaine) hydrochloride monohydrate 42.66 mg/mL equivalent to lidocaine hydrochloride 40 mg/ml (4% w/v)
- Tetracaine (amethocaine) hydrochloride 5.0 mg/mL (0.5% w/v)
- Adrenaline (epinephrine) acid tartrate 18 mg/mL (0.18% w/v) (i.e., 0.1% w/v adrenaline 1 m/mL)

5. Proposed dose and method of administration:

Overall, it is considered that the totality of the submitted data support the dose and administration regimen proposed by the sponsor.

The Sponsor commented that, in practice, dosing is likely to be defined by ED protocols. The Sponsor stated that the proposed product information (PI) is based on the dosage used in the published primary and supportive clinical trials which used a LAT gel.

In general, the studies recommended a minimum time of 20 minutes for contact of the gel with the wound up to a maximum time of 30 minutes. However, in *White 2004* the wound was covered with the gel for 45 minutes and in *Harman 2013* the wound was covered for a minimum of 45 minutes and not longer than 120 minutes. Most studies observed effective anaesthesia within 20 minutes.

In most cases, the recommended dose was based on the size of the laceration (e.g., 0.5 mL/cm). However, the Sponsor stated that for children a weight-based dose, such as 0.1 mL/kg is more appropriate. In *O'Connor 2010,* LAT gel was applied at a dose of 0.5 mL/cm up to 2 mL in children < 3 years and 3 mL in children ≥ 3 years. The Sponsor stated that a maximum dose of 3 mL is also supported for both adolescents and adults, particularly based on the most common presentation available from the hospital pharmacies (i.e., a 3 mL syringe). The Sponsor stated that the proposed PI sets the dose at 0.1 mL/kg for children and 0.5 mL/cm for adults, but with the same maximum doses as recommended by the published clinical studies. The Sponsor states that this is consistent with Australian hospital experience and ED protocols for the administration of topical Laceraine (e.g., the Sydney Children's Hospital Network [SCHN]).

The dose and the method of administration in the proposed PI is:

- Children 1 to 3 years – 0.1 mL/kg to a maximum recommended dose of 2 mL
- Children over 3 years – 0.1 mL/kg to a maximum recommended dose of 3 mL
- Adults and adolescents – 0.5 mL per cm laceration to a maximum recommended dose of 3 mL.

After the wound has been lightly cleaned of surface debris and clotted blood, the recommended dose of gel should be applied to the wound and wound margins, either directly (from the syringe used to draw up the gel) or using a cotton-tipped applicator. The wound should be covered with an occlusive clear film dressing. The use of gauze or island wound dressings is not recommended. The gel and dressing should be left *in situ* for 20 to 30 minutes to a maximum of 60 minutes to avoid prolonged contact and possible absorption. The occlusive dressing should then be removed and the wound cleaned or irrigated to remove residual gel. The duration of

anaesthesia is anticipated to be 45 to 60 minutes following the removal of the gel. Application of the gel to mucous membranes and wounds with end arteriolar supply should be avoided. The gel should be used in one patient on one occasion only and any unused gel should be discarded. Prior to wound repair, sensation should be tested to confirm adequate anaesthesia.

The dose and administration instructions given for the LAT gel in the SCHN guideline is*:*

- 0.1 mL/kg to a maximum of 2 mL for children aged 1 to 3 years
- 0.1 mL/kg to a maximum of 3 mL for age 3 years to adult

The SCHN guidelines advise that wounds should not require volumes greater than the dose limits for lacerations less than 5 cm in length OR 1 mL for each cm of laceration, whichever is the lesser volume. Laceraine should have direct wound contact for a minimum of 20 minutes and a maximum of 60 minutes. The Laceraine dressing and residual product is to be removed after 60 minutes to avoid excess absorption. No more than 4 doses in 24 hours should be prescribed or applied.

The dose and administration instructions given for the LAT solution in the *Therapeutic Guidelines* are:

- the topical solution is indicated for superficial wounds and lacerations less than 7 cm in adults and children 1 year or older;
- 0.1 mL/kg or 1 mL per cm of laceration (whichever is the smaller volume), up to 5 mL;
- soak cotton wool balls in the solution, place on the laceration and hold in place with a dressing. Leave for 20 to 30 minutes (maximum 60 minutes). Do not exceed 4 doses in 24 hours.

Overall, the recommended dosage instructions for Laceraine Gel in the PI, SCHN guidelines and the *Therapeutic Guidelines* are generally consistent.

8. Clinical safety

8.1. Studies providing evaluable safety data

8.1.1. Exposure based on the clinical studies

The submission included 13 clinical studies in patients supporting the efficacy of topical LAT gel for the proposed usage (see Table 3, below). The 13 clinical studies included a total of 1,666 evaluable patients (i.e., 1043 in the LAT group, 623 in the control group). A total of 1043 patients received a LAT combination product, 294 an active control (167 received TAC, 50 lignocaine or lignocaine and adrenaline and 77 adrenaline), 128 received a placebo control and there were 201 historical controls.

Table 3: The 13 clinical studies identified by the Sponsor through the systematic literature search.

	LAT Group			Control Group	
	LAT formulation	LAT strength	Subjects (n)	Comparator	Subjects (n)
Adler 1998	Solution	4, 1 in 1000, 0.5	30	Placebo control	30
Priestly 2003	Solution	4, 1 in 1000, 0.5	84	Adrenaline	77
Schilling 1995	Solution	4, 1 in 1000, 0.5	78	TAC Solution	73
Harman 2013	Gel	4, 1 in 1000, 0.5	105	Placebo control	98
Resch 1998	Gel	4, 1 in 1000, 0.5	91	(LAT solution)	-
	Solution	4, 1 in 1000, 0.5	103		
O'Connor 2010	Gel	4, 1 in 1000, 0.5	196	Historical control	201
Vandamme 2015	Gel	4, 1 in 1000, 0.5	89	No control	-
Siembieda 2022	Gel: single-dose	4, 1 in 1000, 0.5	21	Control group	-
	Gel: triple-dose	4, 1 in 1000, 0.5	27	Intervention group	
Ernst 1995b	Gel	4, 1 in 2000, 0.5	48	TAC Gel	47
Ernst 1997	Gel	4, 1 in 2000, 0.5	33	LA injection	33
White 2004	Gel	4, 1 in 2000, 0.5	67	No control	-
Ernst 1995	Solution	4, 1 in 2000, 0.5	48	TAC solution	47
Lee 2013	Gel	4, 1 in 2000, 0.5	23	Lignocaine injection	17
Totals			**1043**		**623**

Source: Adapted from Table 1, Summary of Clinical Safety
LAT = lidocaine 4%, adrenaline 1:1000 or 1:2000, tetracaine 0.5%
TAC = tetracaine 0.5%, adrenaline 1:2000, cocaine 11.8%

Comment:

It is noted that the exposure data for the number of patients who received a LAT combination product in the 12 clinical studies (excluding Siembieda 2022) provided in Section 2.7.4.1.1 of the *Summary of Clinical Safety (Module 2.7.4)* and Table 1 of Section 2.7.4.1.1 appears to be incorrect. The correct total should be 995 not 955. In the *Clinical Overview – Addendum* Section 2.5.5, the total number of patients exposed to LAT combination treatment in the 14 studies included in the submission is given as 1008. This appears to be incorrect as the total number of patients exposed to

LAT combination treatment in the 14 studies is 1048 (i.e., 1043 patients from the 13 clinical trials in patients plus 5 healthy volunteers from the clinical PK study).

8.1.2. Exposure to Laceraine gel and solution in Australia

The Sponsor stated that Laceraine solution was supplied by Phebra in Australia from July 2004 through to January 2021. Laceraine gel was introduced in August 2020 to a small number of hospitals and replaced the LAT solution from January 2021. The initial pack presentation for Laceraine solution was cartons containing 10 vials. However, during 2008, the pack size changed to cartons of 5 vials. In practical terms 1 vial represents 1 dose or patient treatment. Therefore, it is estimated that the annual number of vials supplied (number of packs x 5) is equivalent to the number of patients treated.

Supply figures, which are only available from the period from 2009 to 2021 inclusive to 30 June 2021, indicate that the use of Laceraine has increased over time from 8,705 vials (patients) per year in 2009 to 35,645 vials (patients) per year in 2021. The total estimated number of vials, or patients treated, is 281,715, comprising 264,720 vials of Laceraine solution and 16,995 vials of Laceraine gel.

The Sponsor stated that, to date, there have been no reports received by Phebra of adverse effects or adverse drug reactions to Laceraine (either solution or gel). Therefore, given the sales figures indicate a total number of vials to June 2021 equivalent to 281,715 patients treated (and a possible additional usage from 2004 – 2008 of 32,000 vials; 4 years of approximately 8,000 vials) the Sponsor concludes that the absence of reported adverse events indicates a very safe product.

8.1.3. Demographics

Of the 13 submitted clinical trials, there were 8 trials exclusively in children and adolescents comprising 161 patients aged 1-17 years in *Priestley 2003*, 151 patients aged 1-17 years in *Schilling 1995,* 203 patients aged 3 months to 17 years in *Harman 2013*, 194 patients of unspecified age range in *Resch 1998*, 397 patients aged ≤ 14 years in *O'Connor 2010*, 95 patients aged 5 to 17 years in *Ernst 1995b,* 67 patients aged 5 to 18 years in *White 2004,* and 48 patients aged 7 to 17 years in *Siembieda 2022.* Of the 1,666 evaluable patients in the 13 studies, 1316 (79.0%) were exclusively children and adolescents. The majority of patients in the 13 studies were male.

Of the 1043 evaluable patients treated with a LAT combination product, 820 (78.6%) were exclusively children and adolescents (Priestley 2003, Schilling 1995, Harman 2013, Resch 1998, O'Connor 2010, Ernst 1995b, White 2004, Siembieda 2022), 48 (4.6%) were exclusively adults (Ernst 1995), and 175 (16.8%) were a mixed population of children, adolescents and adults (Adler 1998, Vandamme 2015, Ernst 1997 and Lee 2013).

8.2. Adverse events

8.2.1. Potential adverse reactions

Potential adverse reactions to topical local anaesthetics include local responses (rash, stinging) and systemic allergic reactions (diffuse swelling, difficulty breathing, and anaphylaxis). An overdose of topical local anaesthetics may adversely affect the cardiovascular or central nervous system. Untoward effects resulting from high systemic levels of local anaesthetics include hypotension, cardiac arrhythmias (bradycardia, ventricular fibrillation, and asystole), light-headedness, double vision, a metallic taste, drowsiness and seizures (published data referred to in Tayeb 2017).

8.2.2. Safety findings reported in the 13 clinical studies included in the submission

Of the 13 published clinical studies included in the submission, 12 provided information on safety findings. No systemic, unexpected or clinically significant safety signals were identified in the studies. Overall, adverse events were infrequently reported in the 13 clinical studies with 1,666 evaluable patients. Most of the adverse events appeared to be complications of the suturing procedure (e.g., wound infection, wound dehiscence) rather than true adverse events related to topical application of LAT. The safety findings as reported in the studies are summarised below in Table 4.

Table 4: Safety findings reported in the submitted clinical studies.

Study	Safety findings as reported in the studies
Adler 1998	No adverse effects were noted after the application of either LAT or placebo solution while the patient was in the ED. Telephone follow-up was achieved for 54 of 60 patients (2 in the LAT group and 4 in the placebo group could not be contacted). There was 1 report of a wound infection in the LAT group. The infection was reported in a patient with a hand laceration. It did not result in either hospitalisation, treatment with IV antibiotics, or wound dehiscence. No other problems or complications were reported in either the LAT of placebo group.
Priestly 2003	There were no observed complications relating to prolonged periods of LAT contact with wounds. Duration of application of LAT to wounds ranged from 20 to 125 minutes, with preservation of wound anaesthesia and no observed complications.
Schilling 1995	No adverse effects were noted after application of either anaesthetic solution (LAT or TAC) or during suturing in any patients.
Harman 2013	No reported adverse effects were reported in the LAT or placebo groups when assessed by physicians in the ED or during the telephone survey at 2 weeks' follow-up.
Resch 1998	No adverse effects were noted in the 194 patients in the LAT groups during the procedure. Post-treatment follow-up was obtained for 181 of the 194 patients (93%). Of the 13 patients who were not able to be contacted, 8 were in the LAT gel group and 5 in the LAT solution group. One patient in each study group sought medical care for a wound infection.
O'Connor 2010	No adverse events were noted with the use of LAT gel in 63 patients.
Vandamme 2015	No complications were reported in the study population treated with LAT gel.
Ernst 1995b	No adverse effects were observed with either LAT or TAC during the procedure. Follow-up was available in 85 of 95 patients entered in the study. There was one wound infection in the TAC group and one in the LAT group. No other problems or complications were reported in either the TAC or LAT groups.
Ernst 1997	Follow-up was available in 75% of the patients, with equal rates in the topical and injectable groups. No complications or wound infections were reported.
White 2004	No complications were reported in the study. No signs of digital ischaemia were found in the 67 cases during the ED visit (0% [95% CI: 0.0% to 5.4%]). Ninety-three percent (62/67) of all patients enrolled were followed up with a phone call 3 to 5 days after laceration repair. There were no reported cases of ischaemia or infection.
Ernst 1995	No adverse effects were reported in either the LAT or TAC groups. Follow-up was available for 91 of 95 patients. There was one wound infection in the TAC group and

	one report of a haematoma in the TAC group without infection. Otherwise, no problems or complications were reported in either the TAC or LAT groups.
Lee 2013	Wound infections were reported in 5 (20%) patients in the LAT gel group and 2 (14.3%) patients in the lignocaine infiltration group; wound dehiscence was reported in 1 (4%) patient in the LAT group and no patients in the lignocaine infiltration group; and lost stitches were reported in 1 (4%) patient in the LAT gel group and no patient in the lignocaine infiltration group.
Siembieda 2022	No reference to safety outcomes could be identified in the study report

Source: Individual study reports.

Comment:

In Table 4 presented in the *Summary of Clinical Safety (Module 2.7.4)*, the results given *for Ernst 1995b* and *Ernst 1997* are incorrect and should be the other way around. In addition, it was stated for *Lee 2013* that there were no adverse events reported. However, complications were reported, which are likely to be complications of the suturing procedure rather than true adverse events associated with topical LAT gel or lignocaine infiltration.

8.3. Clinical laboratory evaluations

None of the 13 published clinical studies included in the submission investigated the effects of topical LAT formulations on clinical laboratory tests. It is considered that evaluation of laboratory tests is not required to support approval of topical LAT gel for the proposed usage.

8.4. Vital signs

None of the 13 published clinical studies included in the submission investigated the effects of topical LAT formulations on vital signs. It is considered that evaluation of vital signs is not required to support approval of topical LAT gel for the proposed usage.

8.5. Safety in special populations

Topical LAT formulations have been assessed in children, adolescents and adults. No safety data specifically referring to children aged ≤ 1 year or adults aged ≥ 65 years could be identified. There were no safety data in patients from different racial backgrounds. There were no data in patients with cardiovascular, neurological, hepatic or renal disease. The proposed PI includes satisfactory *Special Warnings and Precautions for Use*.

8.6. Drug interactions

There were no data exploring drug-drug interactions between topical LAT formulations and other drugs. This is acceptable given the proposed usage for topical LAT gel. The proposed PI includes a statement indicating that the potential for interactions between LAT gel and other medicines is unknown.

8.7. Proposed contraindications

The contraindications for LAT gel listed in the proposed PI are comprehensive and are consistent with the exclusion criteria in most of the clinical studies. However, there is an important contraindication relating to the use of LAT gel in **digits** that has not been listed in the

PI. The proposed PI includes contraindications of LAT gel for *"wounds with end arteriolar supply due to vasoconstriction and risk of ischemia: including ear pinnae, tip of the nose and penis"*.

The Sponsor excluded digits as a contraindication because two of the submitted studies specifically included patients with lacerations on the fingers and/or toes and in neither study was digital ischaemia reported as an adverse event: *White 2004* (fingers in 67 children and adolescents aged 5 to 18 years) and *Vandamme 2015* (finger/toes in 30 adult patients).

However, standard clinical advice is that the use of local anaesthetics containing adrenaline should be avoided when repairing lacerations of the fingers or toes because of the potential risks of ischaemia due to vasoconstriction. *The Sydney Children's Hospitals Network* guideline for the application of Laceraine in the ED includes the use of LAT gel as a contraindication for lacerations on the digits (i.e., *wounds with end arteriolar supply due to vasoconstriction and risk of ischaemia: includes digits, ear pinnae, tip of the nose and penis).* In addition, the PI for lidocaine (lignocaine) hydrochloride and lidocaine (lignocaine) hydrochloride and adrenaline (epinephrine) acid tartrate specifically contraindicates solutions with adrenaline for local analgesia in parts of the body with compromised blood supply or supplied by end arteries, such as fingers, toes, nose, ears or penis as there is a possibility of producing arterial vasoconstriction and subsequent ischaemic gangrene distal to the site of injection. In the context of what appears to be current standard Australian clinical practice for the use of local anaesthetics, it is recommended that Laceraine gel be contraindicated for wounds involving the digits

8.8. Evaluator's overall conclusions on clinical safety

The totality of the submitted data indicates that the safety of LAT gel for the proposed usage is satisfactory. The risks of treatment with LAT are acceptable for the proposed usage.

9. Clinical comments on the product documentation

9.1. Proposed Product Information (PI)

- The proposed PI is generally acceptable. However, the list of *Contraindications relating* to "*wounds with end arteriolar supply due to vasoconstriction and risk of ischemia*" should include digits (fingers and toes) for the reasons given above in Section 8.7.
- Under *Pharmacodynamic Properties (Clinical trials)* it is stated that no data are available. This is not strictly correct. The submitted published clinical trials indicate that the benefit-risk balance for LAT gel for the proposed usage is favourable.
- The proposed PI should use consistent Australian spelling for "ischaemia" throughout the document.

9.2. Proposed Consumer Medicine Information

- In Section 2 (*Do not apply Laceraine Gel Topical Wound Anaesthetic if:*), please add fingers or toes to the 4th dot point.

10. Recommendation regarding authorisation

The benefit-risk balance for LAT gel for the proposed usage is considered to be favourable. Therefore, it is recommended that Laceraine Gel Topical Wound Anaesthetic be approved for:

> **topical application to superficial wounds and lacerations to provide localised surface anaesthesia for wound closure. It may be used to provide topical anaesthetic relief for cleaning, irrigation and debridement of painful minor wounds.**

It is recommended that consideration be given to scheduling Laceraine gel as a prescription only medicine rather than an OTC medicine. This medicine should only be used by medical or nurse practitioners for suturing lacerations. There are a number of significant contraindications that need to be taken into account when using the medicine. There are concerns that OTC availability has the potential for the medicine to be used inappropriately (e.g., burns, abrasions, leg ulcers, mouth ulcers, dog-bites, deep wounds, and wounds where vasoconstriction might result in ischaemia). It is noted that the authors of the PK study assessing lidocaine absorption from the intact skin under an occlusive dressing for 60 minutes in healthy volunteers recommended that "topical anesthetics - even OTC formulations - be used under the supervision of a healthcare professional to avoid adverse toxic effects and, in rare cases, death" (Oni 2012).

11. References

Adler 1998: Adler AJ, Dubinisky I, Eisen J. Does the use of topical lidocaine, epinephrine, and tetracaine solution provide sufficient anesthesia for laceration repair? *Academic Emergency Medicine* 1998;5(2):108-12.

Ernst 1995: Ernst AA, Marvez Valls E, Nick TG, Weiss SJ. LAT (lidocaine- adrenaline- tetracaine) versus TAC (tetracaine-adrenaline-cocaine) for topical anesthesia in face and scalp lacerations. *American Journal of Emergency Medicine* 1995;13(2):151-4.

Ernst 1995b: Ernst AA, Marve E, Nick TG, Chin E, Wood E, Gonzaba WT. Lidocaine adrenaline tetracaine gel versus tetracaine adrenaline cocaine gel for topical anesthesia in linear scalp and facial lacerations in children aged 5 to 17 years. *Pediatrics* 1995;95(2):255-8.

Ernst 1997: Ernst AA, Marvez-Valls E, Nick TG, Mills T, Minvielle L, Houry D. Topical lidocaine adrenaline tetracaine (LAT gel) versus injectable buffered lidocaine for local anesthesia in laceration repair. *Western Journal of Medicine* 1997;167(2):79-81.

Harman 2013: Harman S, Zemek R, Duncane MJ, Ying Y, Pertich W. Efficacy of pain control with topical lidocaine-epinephrine-tetracaine during laceration repair with tissue adhesive in children: a randomized controlled trial. *Canadian Medical Association Journal 2003.* 185(1):629-634

Lee 2013: Lee J, Laxmikantha N, Ong M, Wong E, Wee J. Comparing lignocaine-adrenaline-tetracaine gel with lignocaine infiltration for anesthesia during repair of lacerations: a randomized trial. *World Journal of Emergency Medicine* 2013;4(4):281–4.

New Zealand Data Sheet: Topicaine.

O'Connor 2010: O'Connor G, Mullarkey C. Topical anaesthesia in children: reducing the need for speciality treatment. *European Journal of Emergency Medicine 2010*. 17:97–100.

Priestley 2003: Priestley S, Kelly AM, Chow L, Powell C, Williams A. Application of topical local anesthetic at triage reduces treatment time for children with lacerations: a randomized controlled trial. *Annals of Emergency Medicine* 2003;42(1):34-40.

Resch 1998: Resch K, Schilling C, Borchert BD, Klatzko M, Uden D. Topical anesthesia for pediatric lacerations: a randomized trial of lidocaine-epinephrine-tetracaine solution versus gel. *Annals of Emergency Medicine* 1998;32(6):693-7.

Schilling 1995: Schilling CG, Bank DE, Borchert BA, Klatzko MD, Uden DL. Tetracaine, epinephrine (adrenalin), and cocaine (TAC) versus lidocaine, epinephrine, and tetracaine (LET) for anesthesia of lacerations in children. *Annals of Emergency Medicine* 1995;25(2):203-8.

Siembieda 2022: Siembieda J, Heyming T, Padlipsky P, Young KD. Triple versus single application of lidocaine, epinephrine, and tetracaine for laceration repair in children. Pediatr Emer Care 2022;38: e472–e474.

SHNC 2021: The Sydney Children's Hospitals Network. LACERAINE® topical wound anaesthetic: application – ED: Procedure. Date effective 1st January 2021.

Tayeb 2017: Tayeb BO, Eidelman A, Eidelman CL, McNicol ED, Carr DB. Topical anaesthetics for pain control during repair of dermal laceration. *Cochrane Database of Systematic Reviews* 2017, Issue 2. Art. No.: CD005364. DOI: 10.1002/14651858.CD005364.pub3.

Therapeutic Guidelines 2021: Topical local anaesthetics for acute pain management.

Todd KH, Funk JP. The minimum clinically important difference in physician- assigned visual analog pain scores. *Acad Emerg Med* 1996; 3:142-146.

Vandamme 2015: Vandamme E, Lemoyne S, van der Gucht A, de Cock P, Patrick van de Voorde P. LAT gel for laceration repair in the emergency department: not only for children? European Journal of Emergency Medicine 2015, 00:000–000 DOI: 10.1097/MEJ.0000000000000298.

White 2004: White NJ, Kim MK, Brousseau DC, Bergholte J, Hennes H. The anesthetic effectiveness of lidocaine-adrenaline-tetracaine gel on finger lacerations. *Pediatric Emergency Care* 2004;20(12):812-5.

12. Supporting information, tables and figures

12.1. Clinical study synopses

12.1.1. Schilling 1995

1. Objectives

The objective of this study was to compare the duration of anaesthesia with lidocaine, epinephrine, and tetracaine (LET) solution to that with tetracaine, epinephrine and cocaine (TAC) solution during suturing of uncomplicated lacerations on the face or scalp in children aged 1 to 17 years.

2. Methods

The study was a prospective, randomised, controlled, double-blind Phase III/IV trial comparing TAC and LET local anaesthetic solutions. All patients were admitted to the emergency department at Minneapolis Children's Medical Center, a university-affiliated private children's hospital in the USA, between June 1992 and May 1993. The study protocol was approved by the Minneapolis Childrens Medical Center Institutional Review Board, and informed parental consent was obtained before enrollment.

Patients were eligible for inclusion in the study if they presented to the ED with an uncomplicated laceration on the face or scalp for which the length of the wound could sufficiently be covered by a sterile 2x2 inch (i.e., 5x5 cm) gauze square. Patients were not eligible to participate in the study if the laceration involved the pinna of the ear or nasal alae, if the wound involved significant injury to an underlying structure (i.e., bone, cartilage, tendon, nerves, vessels, or parotid ducts), if the wound was at risk for infection from a human or animal bite or contaminated with soil or fecal material, if the patient had received or had consumed a sedative agent in the preceding 8 hours, if the patient was uncooperative and pain assessment could not be accomplished, or if the patient presented to the ED without a parent or guardian. Wound depth was not a factor in patient eligibility.

3. Patients – inclusion and exclusion criteria

One hundred seventy-one (171) male and female paediatric patients were enrolled. Each patient had one laceration that required suturing. Five (5) patients were excluded after consent was obtained; 1 had been sedated with midazolam before anaesthetic application; 2 had the anaesthetic solution applied for other than 15 minutes; and data were lost for the other 2 patients. Fifteen (15) patients were withdrawn from the study before the initial 27-gauge needle test when the patient became uncooperative or after discovery of a laceration that had significant injury to underlying structure after irrigation of the wound.

Data were analysed for the remaining 151 patients; 73 were treated with TAC; and 78 received LET. The mean±SD age was 6.2±3.4 years (range 1 to 17 years; median age, 6.0 years). Sixty-nine patients were less than 6 years old. The male-to-female ratio was 1.96:1 (100 versus 51). Age was not recorded in 1 of the 151 patients. The mean suturing time was approximately 3 minutes longer in the TAC group than in the LET group, and patients in the TAC group received on average 1 more suture than patients in the LET group.

The TAC and LET groups are summarised below in Table 1 immediately below.

Table 1: Comparison of TAC and LET groups.

	TAC (n=73)	LET (n=78)	P value
Age (years) mean ± SD	5.9 ± 3.3	6.4 ± 3.4	0.30
Sex, Male : Females	1.4 : 1	2.9 : 1	0.03
Suturing time [α] (min)	15.6 ± 10.4	12.5 ± 8.0	0.08
No. of subcutaneous sutures [α]	1.1 ± 1.1	0.9 ± 1.3	0.35
No. of superficial sutures [α]	5.6 ± 2.8	5.0 ± 2.4	0.20
Total no. of sutures [α]	6.8 ± 3.6	5.9 ± 3.3	0.19

Source: Schilling 1995, Table 2.
a of the 116 patients receiving adequate anaesthesia

4. Treatments

Patients were randomised to topical aqueous solutions of TAC (n=73) or LET (n=78):

- Tetracaine 0.5%, adrenaline 0.05%, and cocaine 11.8% (TAC) as a 3 mL dose;
- Lidocaine 4%, epinephrine 0.1%, and tetracaine 0.5% (LET) as a 3 mL dose

Single-doses of the test solutions (3.0 mL) were first painted into the wound with a cotton-tipped swab. The remainder of the 3.0 mL dose was then poured onto a sterile 2x2 inch (5x5 cm) gauze square and held in place for 15 minutes by tape or by the parent's hand. The time immediately after removal of the anaesthetic solution from the wound was considered time 0. After application of the anaesthetic solution, the laceration was irrigated with 100 ml of a 1:10 dilute povidone-iodine solution. Within 5 minutes of removal of the anaesthetic solution, the wound margin was probed with a 27-gauge needle to test the effectiveness of anaesthesia before suturing. Verbal or nonverbal signs of pain were assessed.

5. Randomisation and blinding

The study report stated that the solution was “assigned random numbers” and administered double-blind.

6. Efficacy endpoints

The criteria for assessment included pain assessment (adequacy of anaesthesia before suturing) and effectiveness of anaesthesia (complete, partial, or incomplete). The study outcomes are summarised below in Table 2. All patients were monitored for verbal or nonverbal signs of pain during suturing.

Table 2: Study outcomes.

Classification	Definition
Adequacy of anesthesia	
Adequate	No painful response* is noted when the wound margin is probed with a 27-gauge needle before suturing.
Inadequate	A painful response is noted when the wound margin is probed with a 27-gauge needle before suturing.
Duration of Anesthesia	
Complete	Suturing finished without supplemental lidocaine or a painful response requiring supplemental lidocaine at least 30 minutes after removal of the anesthetic solution from the wound.
Partial	Painful response requiring supplemental lidocaine between 15 and 30 minutes after removal of the anesthetic solution from the wound.
Incomplete	Painful response requiring supplemental lidocaine within 15 minutes after removal of the anesthetic solution from the wound.

*Painful response was considered a sudden grimace or wince, pulling away, or increase in intensity of the patient's cry that occurred simultaneously with the touch of the 27-gauge needle.

Source: Schilling 1995, Table 1.

7. Sample size and statistical methods

Descriptive statistics were used to characterise the study population. The proportion of those patients who had adequate or inadequate anaesthesia within the first 5 minutes after removal of the anaesthetic solution from the wound and the proportion of those patients who experienced complete, partial, or incomplete anaesthesia during suturing were analysed with χ^2 statistics with Yates' correction where appropriate. Fisher's exact test was used when the expected number of occurrences in a group was less than 5. Continuous measures, such as total time of effective anaesthesia with each solution, total suturing time, number of subcutaneous sutures placed, number of superficial sutures placed, and total number of sutures placed, were compared with the two-tailed t-test.

8. Efficacy outcomes

- In the TAC and LET groups combined, 116 of the 151 patients (76.8%) received adequate anaesthesia before suturing. There was no difference between TAC (79.5%) and LET (74.4%) when the proportion of those who had adequate anaesthesia were compared (χ^2, p=0.46).
- Duration of anaesthesia during suturing was classified in 115 of the 116 patients who had adequate anaesthesia. After laceration repair, the physician rated anaesthetic effectiveness (complete, partial or incomplete based on the requirement for supplemental lidocaine). There was no difference between TAC and LET when the proportions of patients defined as complete, partial, or incomplete were compared (χ^2, p=0.18). None of the patients who experienced complete anaesthesia required

supplemental lidocaine for more than 30 minutes after removal of the anaesthetic solution from the wound. In the TAC vs LET groups, complete response was reported in 75.9% (n=44) and 82.4% (n=47) of patients, respectively, partial response was reported in 15.5% (n=9) and 5.3% (n=3) of patients, respectively, and incomplete response was reported in 8.6% (n=5) and 12.3% (n=7) of patients, respectively.

- For patients who experienced adequate anaesthesia before suturing, the mean±SD total time of effective anaesthesia was 18.7±8.8 in the TAC group and 18.0±10.4 minutes in LET group; p=0.71. For patients who experienced complete anaesthesia during suturing, the mean±SD total time of effective anaesthesia was 19.18±9.33 in the TAC group and 19.23±10.8 minutes in the LET group; p=0.98.
- The specific location of the lesion was recorded in 148 patients. Location was divided into 3 groups: scalp, forehead/eyebrow, and cheek/chin. Most lesions were found on the forehead or eyebrow (49.3%). Lesions on the scalp accounted for 30.4% of all lacerations, and 20.2% of the lesions were located on the cheek or chin. There was no difference between TAC and LET in the adequacy of anaesthesia before suturing or duration of anaesthesia during suturing of lesions located on the forehead/eyebrow or scalp area. A statistical difference was identified between TAC and LET in the duration of anaesthesia experienced during suturing of lacerations on the cheek or chin area (p=0.04).
- Analysis of the ED personnel who placed sutures during the study revealed no interrater difference when evaluating adequacy of anaesthesia before suturing (p=0.73) or duration of anaesthesia during suturing (p=0.06).
- The adequacy and duration of anaesthesia by age (< 6 years vs ≥ 6 years) are summarised below in Table 3. In children < 6 years old there was no significant difference between TAC and LET in either adequacy of anaesthesia (before suturing) or duration of anaesthesia. In patients > 6 years more LET patients experienced incomplete anaesthesia and therefore a statistical difference was found favouring TAC over LET (χ^2 p=0.01).

Table 3: Comparison of adequacy and duration of anaesthesia by age.

	<6 Yr			≥6 Yr		
	TAC	**LET**	***P***	**TAC**	**LET**	***P***
No. of patients	35	34		37	44	
Inadequate anesthesia	4 (11)	9 (26)	NS	11 (30)	11 (25)	NS
Adequate anesthesia	31 (89)	25* (74)		26 (70)	33 (75)	
Duration:						
Complete	24† (77)	22 (92)	NS	19† (73)	25 (76)	<.001
Partial	2 (6)	1 (4)		7 (27)	2 (6)	
Incomplete	5 (7)	1 (4)		0 (0)	6 (18)	

Values are numbers of patients (%).
*Duration of anesthesia is classified in only 24 of 25 LET patients <6 years old who experienced adequate anesthesia.
†The age of one TAC patient who experienced complete anesthesia could not be determined.

Source: Schilling 1995, Table 3. Note: In Table 3 of the report, statistical significance for comparison between the two groups for duration of adequate anaesthesia is given as p < 0.001, which is inconsistent with the narrative text which gives a p-value of 0.01.

9. Safety

No adverse effects were noted after application of either anaesthetic solution or during suturing in any patients during this study.

10. Evaluator's comments - strengths and limitations

This was a good quality, randomised, double-blind, active-control clinical trial. Overall, the clinical data were comparable for the LET and TAC solutions. The active control (TAC) is considered to be appropriate. The two treatment groups were reasonably well balanced. The study used subjective assessment of the initial adequacy and duration of anaesthesia based on the physician's assessment of the patient's verbal and non-verbal response. This is reasonable given that that the mean age of the patients was approximately 6 years. There was no sample size calculation for the primary objective comparing the duration of anaesthesia experienced with LET compared with TAC during suturing of uncomplicated lacerations on the face or scalp. However, the duration of anaesthesia in those patients who achieved complete anaesthesia during suturing was reported in a numerically greater proportion of patients in the LET group than in the TAC group (82.4% vs 75.9%, respectively). A statistical difference between the two treatment groups was identified for the duration of anaesthesia experienced during suturing of lacerations on the cheek or chin area, but the numerical values for the duration of anaesthesia could not be identified.

The limitations of the study included the subjective method of pain assessment, the use of more than one clinician for suturing, and no formal follow-up collection of adverse event data. The study report provided an adequate description of the steps taking to minimize the effects of the identified limitations.

The study was included in the Cochrane Review (Tayeb 2017).

12.1.2. Ernst 1995

1. Objectives

The study objective was to compare the topical anaesthetic LAT with TAC for efficacy, adverse effects, and costs in adults with facial or scalp lacerations.

2. Methods

The study was approved by the Louisiana State University Institutional Review Board (USA) and was performed in a county facility. The design was a prospective, randomised, controlled, double-blind study. Adults patients were included if they had lacerations located on the face or scalp, the laceration size was 7 cm or less in length, and there was no mucosal involvement.

3. Patients

One hundred (100) adult patients were initially entered in the study (50 in each of the two treatment groups). Four (4) patients were excluded before analysis because they were considered treatment failures as they required additional injected lidocaine (3 in the TAC group and 1 in the LAT group). A fifth patient was excluded because of improper data collection (LAT group). Ninety-five (95) patients were included in final statistical analysis with 48 receiving LAT and 47 receiving TAC. The demographics of the patients in the two treatment groups were well balanced. The demographics of the patients are summarised below in Table 1.

TABLE 1. Demographics

	LAT (n = 48)	TAC (n = 47)
ED/Treatment Failures	2	3
Sex		
Males	40	36
Females	9	14
Ages (mean ± STD)	33 ± 11	34 ± 13
Length of laceration (mean ± STD)	2.6 ± 1.2	2.3 ± 0.8
Amount of local anesthetic used (mean ± STD)	1.6 ± 0.9	1.6 ± 0.8
Location of laceration		
Face	41	40
Scalp	7	6
Number of sutures placed		
Median	6	6
Range	1-22	2-18

Source: Ernst 1995, Table 1. Note: The demographic table provided in the study report (Table 1) did not give units for the length of the laceration or the volume of local anaesthetic administered, although these appear to be cm and mL, respectively.

4. Treatments

The solutions were prepared by a pharmacist and were available in coded sterile, capped 3-mL syringes with a cotton ball for application.

The TAC solution was a standard 0.5% tetracaine, 1:2000 epinephrine, 11.8% cocaine; 47 patients randomised to this group

The LAT solution was prepared as 4% lidocaine, 1:2000 epinephrine and 1% tetracaine; 48 patients randomised to this group.

Both TAC and LAT were clear solutions mixed from powders.

After consent was obtained, wounds were prepared based on the preference of the physician. Topical solutions were applied with small saturated pieces of cotton formed to fit into and around the wound edges and mild pressure was applied. Solutions remained on the wound a

minimum of 10 minutes to a maximum of 30 minutes. The wound was rechecked every 10 minutes until the 30-minute time limit. If anaesthesia was still not adequate, this was recorded, then 1% lidocaine was injected and the amount recorded. After the anaesthesia was considered adequate, laceration repair was performed as deemed suitable by the physician.

5. Randomisation and blinding

Treatments were randomised according to a random numbers table. Patients and physicians performing wound closure were blinded to the treatment solutions being used.

6. Efficacy endpoints

Both physician and patient rated the anaesthesia effectiveness during wound closure utilising a standard 10-cm linear visual analog scale (VAS) with 0 corresponding to no pain and 10 to worst possible pain. Physician rating was based on patient response to the needle and/or request for more anaesthesia by the patient.

Patients also reported the number of sutures causing pain, which was analysed as percentage of total sutures placed. Demographic and clinical data were collected in the emergency department (ED) at the time of suturing. These included age, sex, length of lacerations, location of laceration, amount of local anaesthetic used, the need for additional lidocaine injectable anaesthesia, whether anaesthesia lasted throughout the entire procedure, and any complications at the time of suturing. Patients were followed by return visits, medical records, or telephone for any problems with healing of lacerations.

7. Statistical methods

Statistical methods included medians, ranges, and Interquartile Ranges (IQR). Wilcoxon's ranked sum test was used in determining if continuous variables (age, length, and amount) of solutions were equally distributed among the categorised response variables (percentage causing pain and separate VAS ratings of physicians and patients). Fisher's exact test was used to determine if the discrete variables (male versus female and location of laceration) were equally distributed for each categorical response variable (percentage of sutures causing pain, VAS ratings of physicians, and VAS ratings of patients). To assess treatment effects on percentage of sutures causing pain and VAS ratings, the Wilcoxon's ranked sum test was used. To evaluate agreement between patient and physician responses in VAS ratings, generalised kappa statistics were used. For all analyses, $p < 0.05$ was considered statistically significant.

A power analysis was performed on the two groups to determine adequate sample size in determining a difference between the two groups, LAT versus TAC. A sample size of 95 had a power of 0.8 to tell a ranked sum difference of 15.

8. Efficacy outcomes

- ***Sutures causing pain according to the patients***

The percentage of sutures causing pain based on patient assessment are summarised below in Table 2.

TABLE 2 Percentage of sutures causing pain

	LAT	TAC
Median percentage of sutures causing pain	0	0
Range of percentage of sutures causing pain	0 to 0.33	0 to 0.8
Mean ranked sum	42.8	53.3

NOTE: $P = .036$ for differences between LAT versus TAC percentage causing pain.

Source: Ernst 1995, Table 2.

- ***VAS ratings for physicians and patients***

The VAS ratings for physicians and patients are summarised below in Table 3.

TABLE 3. Pain scores in the LAT versus TAC groups

	LAT	TAC
Physician ratings		
Median	0	1
Range	0 to 5	0 to 6
Mean ranked sum*	41.6	54.6
Patient ratings		
Median	0	0
Range	0 to 4	0 to 6
Mean ranked sum†	45.3	50.8

* $P = .0093$ for difference between LAT and TAC according to physicians.
† $P = .266$ for difference between LAT and TAC according to patients.

Source: Ernst 1995, Table 3.

- ***Physician and patient agreement***

It was reported in the study that, using a weighted kappa statistics analysis, general agreement was found between physician and patient VAS ratings for the LAT versus TAC groups. For overall agreement in the two groups, 73% matched exactly. Subdividing into LAT and TAC groups, 79% of LAT physician and patient scores matched exactly, with a weighted kappa score of 64%. For the TAC group, 66% matched exactly, with a weighted kappa score of 64%. These were reported to be equivalent on analysis.

- ***Treatment failures***

Four (4) patients were excluded before analysis because they required additional injected lidocaine. They were considered treatment failures because of inadequate anaesthesia (3 in the TAC group and 1 in the LAT group).

9. Safety outcomes

Follow-up was available for 91 of 95 patients. There was one wound infection in the TAC group and one report of a haematoma in the TAC group without infection. Otherwise no problems or complications were reported in either TAC or LAT groups.

10. Evaluator's comments – strengths and limitations

This was a good quality, randomised, double-blind, active-control clinical trial. The dates of the study were not provided. The active control (TAC) is considered to be appropriate. The abstract included the following statements: "Patients stated the number of sutures causing pain and patients and physicians rated the overall pain of suturing using a standard visual analog scale (VAS). The power of the study to determine a ranked sum difference of 15 was 0.8". This suggests that the ranked sum difference of 15 used to calculate the sample size might refer to each of the listed efficacy parameters.

The percentage of sutures causing pain were statistically significantly lower in the LAT group than in the TAC group. There were no statistically significant differences between the two treatment groups for the VAS pain scores associated with suturing when rated separately by physicians and by patients. Overall, the study showed that LAT was a better topical anaesthetic for the repair of superficial lacerations of the face or scalp in adults.

The study reported the following limitations: (1) lack of standardisation of method of preparation of wounds and type or size of suture material used; (2) failure to document the amount of time to achieve adequate anaesthesia of each wound; (3) a discrepancy between physician and patient ratings of pain, but the additional measure of percentage of sutures causing pain was regarded as helpful in determining adequate anaesthesia of the solutions according to the patients; and (4) only adults were included in the present study because it was believed that pain ratings would be more accurate in these patients than in children.

The study was included in the Cochrane Review (Tayeb 2017).

12.1.3. Ernst 1995b

1. Objectives

The study objective was to compare LAT gel to TAC gel for efficacy, side effects, and costs in children aged 5 to 17 years with facial or scalp lacerations.

2. Methods

The study was undertaken in the USA. The study was approved by the Louisiana State University Institutional Review Board and was performed in a county facility. The design was a prospective, randomised, double-blinded clinical trial. One hundred (100) patients aged 5 to 17 years were to be entered, 50 to receive TAC and 50 to receive LAT. Following informed consent, patients were included if they had lacerations located on the face or scalp, the laceration size was 7 cm or less in length, and there was no mucosal involvement. Patients were excluded if they were believed to be unable to measure pain via a modified multidimensional pain rating scale specifically for children (rated from 0 corresponding to no pain to 10 corresponding to worst pain ever), secondary to alcohol or drug use, mental illness, if they had allergies to ester or amide anaesthetics, or if they had contraindications to vasoconstrictor use or lacerations were more than 8 hours old or grossly contaminated.

3. Patients

One hundred (100) patients were initially entered in the Study: 5 patients were excluded before statistical analysis because each required additional lidocaine to be injected and pain scales were not considered useful in judging pain. These 5 patients were considered treatment failures due to inadequate anaesthesia (3 in the TAC group and 2 in the LAT group). Ninety-five (95) patients were included in the final statistical analysis, with 48 receiving LAT and 47 receiving TAC. There were no differences in demographic data between the two groups. Distribution of ages, amount of gel used, length of lacerations, sex of patients, and locations of lacerations was similar for the two groups (see Table 1 below).

TABLE 1. Demographics

	LAT (n = 48)	TAC (n = 47)	p-value
ED/treatment failures	2	3	
Sex			
Males	38	34	
Females	10	13	.48*
Ages			
Median	7	8	
Range	5–16	5–17	
Interquartile range	10–5.5	12–6	.18‡
Length of laceration			
Median	2.0 cm	2.0 cm	
Range	0.5–5 cm	0.5–4 cm	
Interquartile range	2.5–1.25 cm	2.5–1.0 cm	.95‡
Volume of local			
Mean	1.5 ± 0.8	1.5 ± 0.35	
Median	1.40 cc	1.25 cc	
Range	0.25–3 cc	0.25–3.0 cc	
Interquartile range	2.0–1.0 cc	2.0–1.0 cc	.89‡
Location of laceration			
Face	34	30	
Scalp	14	17	.72*
Number of sutures placed			
Median	5	4	
Range	1–13	1–15	.66‡

* Using Fisher's exact test.
‡ Using Wilcoxon's rank sum test.

Source: Ernst 1995b, Table 1.

4. Treatments

The TAC gel was a standard combination of 0.5% tetracaine, 1:2000 epinephrine, and 11.8% cocaine: 47 patients were randomised to the TAC group.

The LAT gel was a combination of 4% lidocaine, 1:2000 epinephrine, and 0.5% tetracaine: 48 patients were randomised to the LAT group.

Hydroxyethyl cellulose with preservatives was used in both gels. The gels were prepared by a pharmacist from dried ingredients mixed with water and added to the hydroxyelthylcellulose gel. The final concentration of cocaine in the TAC solution was 118 mg/mL with 40 mg/mL of lidocaine in LAT. Sterile water was added to appropriate volume. The gels were available in sterile capped 3 mL syringes with a cotton-tipped applicator for usage.

After informed consent was obtained, wounds were prepared based on the preference of the physician. Topical gels were applied by cotton-tipped applicators into and around the wound edges. Gels remained on the wound a minimum of 10 minutes to a maximum of 30 minutes. Care was taken not to apply gel too near mucous membranes. If the patient was still sensitive to pinprick with a 25-gauge needle at 10 minutes, more time was given. If the wound was still sensitive at 20 minutes, more of the same gel could be applied. The wound was rechecked every 10 minutes to the 30-minute time limit. If the wound was still sensitive to pinprick with a 25-gauge needle, this was recorded, then 1% lidocaine was injected and the amount recorded. After the anaesthesia was felt to be adequate, laceration repair was performed as deemed suitable by the physician.

The mean amount of gel used in both the TAC and the LAT groups was 1.5 mL corresponding to 177 mg of cocaine for TAC and 60 mg of lidocaine for LAT. No patient in either group required more than one application of TAC or LAT.

5. Randomisation and blinding

Gels were randomised according to a random numbers table Patients and physicians were blinded to the gel being used.

6. Efficacy endpoints

Physicians were instructed in use of the pain scale before the study and again at the time of patient entry. Both physician and patient or parent rated the anaesthesia effectiveness during suturing utilising a modified multidimensional pain scale (0 for no pain and ending with 10 for worst pain). In addition, patients or parents reported the number of sutures causing pain, which was analysed as percent of total sutures placed.

7. Statistical methods

A power analysis was performed on the two groups to determine adequate sample size in determining a difference between the two groups, TAC versus LAT. A sample size of 95 had a power of 0.8 to determine a ranked sum difference of 15.

A total of 95 patients were included in the statistical analysis with 47 receiving TAC and 48 receiving LAT. Wilcoxon's ranked sum test was employed in determining if continuous variables (age, length, and amount) of solutions were equally distributed for each of the categorised response variables (percent causing pain and multidimensional scale ratings of physicians and of patients). Fisher's exact test was used to determine if the discrete variables (male versus female and location of laceration) were equally distributed for each categorical response variable (percent of sutures causing pain, interval scale ratings of physicians, and pain ratings of patients). To assess treatment effects on percent of sutures causing pain and the pain scale ratings, Wilcoxon's ranked sum test was used. For all analyses $p < 0.05$ was considered to be statistically significant.

8. Efficacy outcomes - results

- ***Patients/parents assessment of sutures causing pain***

The percent of sutures causing pain in each of the treatment groups based on patient/parent assessment is summarised below in Table 2. No statistically significant or clinically significant differences were detected in the LAT versus TAC groups (p=0.51).

TABLE 2. Percent of Sutures Causing Pain

	LAT	TAC
Mean % of sutures causing pain	18	13
Median % of sutures causing pain	0	0
Range of % causing pain	0–100	0–100
Interquartile range of % causing pain	0–25	0–20
Mean ranked sum*	49.57*	46.39*

* P = .51 for differences between LAT versus TAC percent causing pain (using Wilcoxon's rank sum test).

Source: Ernst 1995b, Table 2.

- ***Physician and patient/parent assessment of pain scores assessed using the multiple dimension scale (0 to 10)***

Pain scores in each of the treatment groups are summarised below in Table 3. No statistically significant or clinically significant differences were observed in the pain scores between the LAT and TAC groups according to the physician's assessment (p=0.80) or the patient's assessment (p=0.71).

TABLE 3. Pain Scores in the LAT Versus TAC Groups

	LAT	TAC
Physician ratings		
Median	2	2
Range	0–7	0–7
Interquartile range	3.0–0.0	3.0–0.0
Mean ranked sum*	48.7*	47.3*
Patient ratings		
Median	2.0	2.0
Range	0–8	0–7
Interquartile range	5.0–0.0	3.0–1.0
Mean ranked sum‡	49.0‡	46.9‡

* P = .80 for difference between LAT and TAC according to physicians.

‡ P = .71 for difference between LAT and TAC according to patients.

Source: Ernst 1995b, Table 3.

9. Safety - results

Follow-up was available in 85 of 95 patients entered in the study. There was one wound infection in the TAC group and one in the LAT group. No other problems or complications were reported in either the TAC or LAT groups.

10. Evaluator's comments – strengths and limitations

This was a good quality, randomised, double-blind, active-control clinical trial. The active control (TAC) is considered to be appropriate. The abstract included the following statements: "Physicians and patients/parents separately rated the overall pain of suturing using a modified multidimensional scale for pain assessment specifically for children. Patients/parents also stated the number of sutures causing pain. The power of the study to determine a ranked sum difference of 15 was 0.8". This suggests that the ranked sum difference of 15 used to calculate the sample size might refer to each of the listed efficacy parameters.

The percentage of sutures causing pain were numerically lower in the TAC group than in the LAT group, but the difference between the two groups was not statistically significant. There were no statistically significant differences between the two treatment groups for pain scores associated

with suturing when rated separately by physicians and by patients/parents. Overall, the study showed that the LAT and TAC gel formulations used in this study were comparable as topical anaesthetics for the repair of superficial lacerations of the face or scalp in children and adolescents.

The study reported the following limitations: "Limitations of our study include small sample sizes that may not be able to detect adverse effects. We did not measure blood levels to substantiate absorption, although the amounts used were well below potentially toxic amounts. We did not standardise the type of suture material and preparation".

The study was included in the Cochrane Review (Tayeb 2017).

12.1.4. Adler 1998

1. Objectives

To determine: (1) the effectiveness of LET solution in eliminating or reducing pain experienced in suturing superficial lacerations in adult patients; and (2) the effectiveness of LET in reducing the pain of local anaesthetic injection.

2. Methods

The study was a randomised, prospective, double-blind, placebo-controlled intervention trial comparing LET solution with placebo (sterile water) for topical wound anaesthesia undertaken in 60 adult patients with superficial lacerations. The study was conducted in the ED of a community-based teaching hospital affiliated with the University of Toronto (Canada). Enrollment occurred over a 3-month period from June 1, 1996, to August 31, 1996. The study was approved by the research committee of the hospital before initiation of the protocol.

Patients were included in the study if they had a superficial laceration (one that could be repaired with a single- layer closure) that was ≤ 7 cm, with no mucosal involvement. No wound sites were excluded, although the majority of lacerations were on the hands. Subjects were excluded for the following reasons: age < 12 years, intoxication with alcohol or other substances of abuse, allergy to any of the agents being used, wounds > 8 hours old, grossly contaminated wounds, or history of a cardiac, respiratory, or neurologic disorder. Subjects also were excluded if they were unable to measure pain via a standard visual analog scale (VAS).

3. Patients

Sixty patients were entered in the study. Thirty patients were treated with LET; 30 patients received placebo. No significant differences were found in the demographic data between the LET and placebo groups (see Table 1 immediately below).

Table 1: Demographics

	LET (n = 30)	Placebo (n = 30)
Sex		
Males	21	21
Females	9	9
Age—mean ± SD	38 ± 19 yr	41 ± 20 yr
Length of laceration—mean ± SD	2.3 ± 1.3 cm	2.2 ± 1.1 cm
Location of laceration		
Face	4	5
Scalp	2	3
Hand	16	17
Arm	4	2
Leg	4	3
Number of sutures placed—median	4.0	4.0
Suturing time—mean ± SD	12.2 ± 4.2 min	13.1 ± 4.4 min

Source: Adler 1998, Table 1.

4. Treatments

The solutions were prepared by a hospital pharmacist and were available in coded, sterile 5 mL bottles.

- LET solution was prepared as 4% lidocaine, 1: 1,000 epinephrine, and 0.5% tetracaine.

- Placebo solution was sterile water, which was prepared in identical 5 mL bottles to LET. Neither the LET nor placebo solution had a distinctive colour or odour.

After obtaining informed consent, a cotton ball was saturated with 3 mL of LET or placebo. The solution was applied to the wound for a minimum of 20 minutes to a maximum of 30 minutes. Mild pressure was applied to the cotton ball by the patient's gloved hand throughout this period.

5. Randomisation and blinding

The LET and placebo solutions were randomised according to a random numbers table. Patients and medical personnel were blinded to the solutions being used.

6. Efficacy endpoints

Criteria for evaluation of efficacy included: adequacy of initial anaesthesia; patient rated VAS; and requirement for additional local anaesthetic. Within 5 minutes of removal of the anaesthetic or placebo solution, the wound margin was probed with a 27-gauge needle to test the effectiveness of anaesthesia before suturing. The patient rated the anaesthesia effectiveness using a standard 10-cm linear VAS, with 0 corresponding to "no pain" and I0 to "worst possible pain." If no discomfort was experienced with probing of the wound, the anaesthetic effect was defined as adequate and sutures were placed by one of the authors. If any discomfort was experienced with probing of the wound, the anaesthetic effect was defined as inadequate, and 1 % lidocaine (up to 4.5 mg/kg) or 1% lidocaine with epinephrine (up to 7.0 mg/kg) was injected subcutaneously around the wound. For those patients who required additional local anaesthesia, another pain assessment using the same VAS was done to determine the level of pain on injection. All pain assessments were done by 2 of the study authors to ensure consistency. Inter-rater variability was not determined.

7. Statistical methods

All parametric data, as assessed by Bartlett's test, were expressed as mean ± standard deviation. Data were analysed by a 1-way analysis of variance (ANOVA). If a significant result was obtained with the ANOVA, the means of all groups were compared a posteriori using either paired or unpaired t-tests depending on the groups analysed. All nonparametric data were expressed as medians and were analysed by a Kruskal-Wallis ANOVA. When a significant result was obtained with the Kruskal-Wallis ANOVA, the medians of all groups were compared a posteriori using a Mann-Whitney test. Differences between group means/medians were considered statistically significant at $p < 0.05$. No a priori power calculation was performed.

8. Efficacy - results

The outcome measures are summarised below in Table 2.

	LET (n=30)	Placebo (n=30)	P value
Pain scale values to needle probing (cm), median	4.0	5.0	< 0.05
Patients requesting local anaesthetic, No. (%)	13 (43.3)	30 (100)	-
Pain scale values to injection of local anaesthetic (cm), median	(n=13) 3.5	(n=30) 5.0	0.09

Source: results narrative, Alder et al., 1998

Source: Summary of Clinical Efficacy, Module 2.

The level of pain reported by the patient on probing of the wound margin with a 27-gauge needle following application of the study solution was significantly reduced in the LET group vs the placebo group (medians of 4.0 vs 5.0 cm, respectively, $p < 0.05$).

Following application of the LET or placebo solutions, 17 of the 30 patients in the LET group denied the need for further anaesthetic, while all 30 subjects in the placebo group required additional local anaesthesia. The degrees of pain on injection of local anaesthetic, if additional anaesthetic was requested by the patient, were not significantly different between the LET and placebo groups (medians of 3.5 cm vs 5.0 cm, respectively, p=0.09). However, since pain-on-injection scores were obtained only from the 13 patients in the LET group who required local anaesthesia, the power to discern a difference between the groups was reduced.

In the LET group, pain scale values on needle probing of the wound were significantly lower in the face/scalp group compared with the extremity group (medians of 0.5 cm vs 4.0 cm, respectively, $p < 0.05$). In the LET group, only 1 of the 6 patients with a face/scalp laceration required an injection of local anaesthetic, while 12 of the 24 patients with extremity lacerations required an injection of local anaesthetic. No significant differences were found between pain scale values in different wound locations in the placebo group.

9. Safety - results

No adverse effects were noted after the application of either the LET or placebo solution while the patients were in the ED. Telephone follow-ups were conducted for 54 of the 60 patients (2 patients in the LET group and 4 patients in the placebo group could not be contacted). There was 1 report of a wound infection in the LET group in a patient with a hand laceration. Otherwise, no problems or complications were reported in either the LET or placebo group.

10. Evaluator's comments – strengths and limitations

This was a good quality randomised, placebo (sterile water) controlled double blind study in adult patients with superficial skin lacerations ≤ 7cm predominantly on the hands. Patients in the LET group experienced significantly less pain on needle probing of the wound following topical application than patients in the placebo group. In addition, a notable numerical difference in favour of the LET group compared with the placebo group was observed in the proportion of patients <u>not</u> requiring additional local anaesthetic following initial application of the topical anaesthetics (i.e., 57 vs 0%, respectively).

In this study, only 2 medical personnel performed suturing and measured pain scale values, thereby limiting variability between measurements. No sample sized calculations were performed in the study. However, the difference between the two treatment groups as regards effectiveness of anaesthesia statistically significantly favoured the LET group compared with the placebo group. The study report identified the following limitations: (1) lack of standardisation of type or size of suture material used; (2) time to achieve adequate anaesthesia not documented; (3) use of vasoconstrictor in LET producing blanching might have resulted in observer bias; (4) only adults were included in the study.

The study was not included in the Cochrane Review (Tayeb 2017). The reasons given for none inclusion were: "Study compared topical lidocaine-epinephrine-tetracaine (LET) only vs placebo. No comparison with infiltrated local anaesthetics or other topical anaesthetics ".

12.1.5. Priestley 2003

1. Objectives

The study objective was to determine whether application of topical local anaesthetic (ALA) at triage reduces total treatment time for children with simple lacerations. The study compared ALA (i.e., adrenaline, lidocaine, and amethocaine) to placebo (adrenaline).

2. Methods

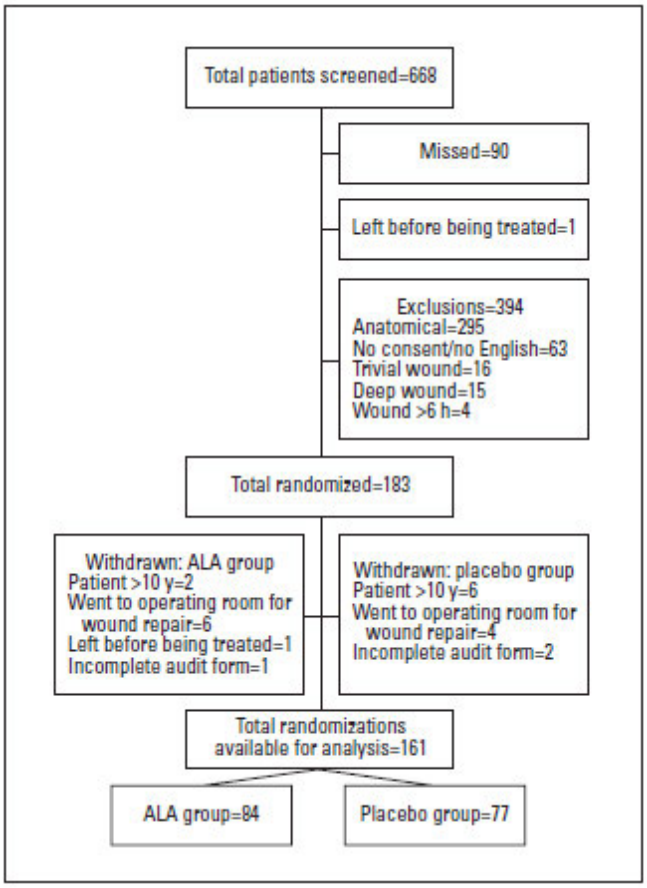
This prospective, randomised, double-blind, controlled trial was conducted in an Australian urban paediatric ED in children aged 1 to 10 years with simple lacerations. The study was undertaken between July 2000 and February 2001. Eligible patients included patients from whom consent had been obtained. The study was approved by the Clinical Research and Ethics Committee, Royal Melbourne Hospital Research Foundation.

Children aged 1 to 10 years with lacerations considered to require wound repair under local anaesthetic were triaged by experienced nursing staff using the National Triage Scale and screened for inclusion in the study. Children were excluded from the study if the wound involved the digits, ears, penis, nose, or mucous membranes; was close to the eye; was a deep wound involving bone, cartilage, tendon, or vessels; was older than 6 hours; or was trivial (unlikely to require repair). Other exclusion criteria included allergy or previous reaction to local anaesthesia, anaesthetic application or infiltration to the area before ED presentation, and failure to obtain informed consent from the child's parent or guardian. Patients were also excluded from analysis if they were admitted for wound repair in the operating suite, their data were incomplete, or they withdrew from the study.

3. Patients

Six hundred sixty-eight children presented to the ED with lacerations. One hundred eighty-three patients were randomised, and 161 cases were eligible for analysis. A flow diagram of patient selection detailing exclusions is shown below in Figure 1. The most common reason for exclusion was the anatomic site of the laceration. Of the 161 cases analysed, 84 children received ALA and 77 received placebo (adrenaline).

Figure 1: Patient disposition



Source: Priestley 2003, Figure 2.

The demographic variables and wound site characteristics of the two treatment groups are summarised below in Table 1. Overall, apart from the gender distribution, the demographic and wound characteristics of the two treatment groups were well balanced.

Table 1: Demographic variables and wound site distribution.

	ALA (n=84)	Adrenaline (n=77)
Sex: males / females	38 / 46	61 / 16
Age (years) median, (range)	4 (1 - 10)	4 (1 - 10)
Wound site, No. (%)		
- Head/face	74 (88)	61 (79)
- Arm/forearm	1 (1)	1 (1)
- hand	3 (4)	3 (4)
- leg	4 (5)	8 (11)
- foot/ankle	2 (2)	3 (4)
- buttock	0	1 (1)
Total	84	77

Source: Tables 1 and 2, Priestley et al., 2003

Source: Summary of Clinical Efficacy, Priestley 2003, Table 6.

4. Treatments

Eligible patients for whom consent was obtained were randomised to receive application at triage of either:

- ALA solution (lidocaine 4%, adrenaline 1:1000 [0.1%], tetracaine 0.5%); or
- Placebo solution (adrenaline 1:1000 [0.1%]).

The Pharmacy Department made up identical vials of the two study agents, each containing 3 mL of clear solution. Medical officers who were blinded to which study solution had been applied assessed the wound and decided on method of repair (Steristrips, glue, or sutures) and whether sedation would be required to achieve adequate wound cleaning and repair. After this assessment, the treating physician was unblinded to the study solution applied. For children who received placebo solution at triage, a decision was then made about using either topical or infiltrated local anaesthesia or no anaesthesia. For the topical local anaesthesia group, the solution remained in contact with the wound until just before repair.

5. Randomisation and blinding

Randomisation was by random number sequence generated independently by the Pharmacy Department, which made up identical vials of the 2 study agents, each containing 3 mL of clear solution. Allocation was by use of the next numbered vial in sequence, and wound application of topical solution was performed uniformly. Medical officers (blinded to study solution) assessed the wound and decided on method of repair (Steristrips, glue, or sutures) and whether sedation would be required to achieve adequate wound cleaning and repair. After this assessment, the treating physician was unblinded.

6. Efficacy endpoints

The primary efficacy outcome measure was the total treatment time (defined as the difference between discharge time and triage time). A secondary outcome was the proportion of children in each group who required sedation.

7. Statistical methods

Sample size was estimated according to a 90% power to demonstrate a 20-minute difference in total treatment time, SD of 30 minutes in treatment time, and a significance level of 0.05. Data analysis was by descriptive statistics, the Mann-Whitney *U* for comparison of treatment times, and χ^2 test comparing sedation rate between the groups.

8. Efficacy - results

The median total treatment time for the ALA group was 77 minutes compared with 108 minutes for the placebo group (effect size 31 minutes; 95%: 15 to 47 minutes; p=0.0019, Mann-Whitney *U* Test).

The distribution of wound closure in the ALA vs placebo (adrenaline) groups, respectively, was:

- None: n=3 (4%) vs n=3 (4%)
- Steristrips: n=2 (2%) vs n=4 (5%)
- Glue: n=51 (61%) vs n=33 (42%)
- Suture: n=27 (33%) vs n=38 (49%)

For the subgroup requiring wound repair by suture, the median treatment time for the ALA group (n=27) was 107 minutes compared with 138 minutes for the placebo group (n=38): effect size 31 minutes; 95% CI: 15 to 71 minutes.

There was an overall adjuvant sedation rate of 14.2% (23/161): 10 (12%) patients in the ALA group and 13 (17%) patients in the placebo group (effect size 5%; 95% CI: –16% to 6%; p=0.46, χ^2).

9. Safety – results

There were no observed complications relating to prolonged periods of LAT contact with wounds. Duration of application of LAT to wounds ranged from 20 to 125 minutes, with preservation of wound anaesthesia and no observed complication.

10. Evaluator's comments – strengths and limitations

This was a good quality randomised, placebo (adrenaline) controlled study in children aged 1 to 10 years. In this study, the LAT group was referred to as the ALA group. The use of adrenaline as placebo had the potential to minimise observer bias between the two treatment group, as blanching due to vasoconstriction following topical application could be anticipated in both the ALA and placebo groups. The study demonstrated that the duration of anaesthesia (treatment time) was statistically significantly reduced in the ALA group compared with the placebo group (effect size 31 minutes). The study was adequately powered to demonstrate a difference in total treatment time between treatment groups of 20 minutes. The study did not identify a statistically significant difference in the need for sedation between the two treatment groups, but the study was not powered to assess this difference. The study did not assess differences in pain scores in order to measure the effectiveness of anaesthesia. Instead, the total treatment time was used as a surrogate for effectiveness.

The study report summarised the limitations of the study as follows: "This study has some limitations that should be considered when the results are interpreted. With 90 patients (13% of lacerations) unscreened for inclusion, this sample is essentially a convenience [sample]. Factors that may have influenced the failure to screen these children are that staff were too busy or simply forgot, which is unlikely to have introduced a systematic bias into the study. The triage nurses involved in this study are experienced. The results may not be generalizable to EDs with triage nurses with lower levels of skill or experience. In addition, the time savings may not be generalizable to departments that have shorter waiting times than the study institution. Observed differences in sex and the use of glue versus suturing may have influenced the results".

The study was excluded from the Cochrane Review (Tayeb 2017), as "outcomes of interest [i.e., pain] were not measured".

12.1.6. Harman 2013

1. Objectives

The objective of the study was to investigate whether pre-applying LET would decrease pain in children during minor laceration repair using tissue adhesive.

2. Methods

The study was a randomised, placebo-controlled, blinded trial in children aged from 3 months to 17 years (inclusive) with a laceration of less than 3 cm in length on the face, torso, trunk or extremities deemed appropriate for tissue adhesive repair by their treating physicians. There were 203 patients included in the analysis, 105 in the LET group and 98 in the placebo group. The patients were recruited from March 2011 to January 2012 from a tertiary-care, academic, paediatric emergency department in Canada. Health Canada approved this regulated phase II clinical trial and the Children's Hospital of Eastern Ontario Research Ethics Board approved the study.

3. Patients

Children aged 3 months to 17 years (inclusive) were eligible for the study if they had a laceration of less than 3 cm in length on the face, torso, trunk or extremities that was deemed appropriate for tissue adhesive repair by their treating physicians. Children were excluded if their wounds required debridement or suturing before a first glue attempt, as were children with wounds caused by an animal (or human) bite or scratch; wounds on the ear, fingers or toes; wounds crossing joint lines or the mucocutaneous junction, or in areas of concentrated hair such as the scalp or eyebrow; puncture or stellate crush wounds; children with a known history of keloid formation or a known allergy to cyanoacrylates; and children taking medications known to impair wound healing or haemostasis. Patients aged 14 years and older provided written informed consent. For children less than 14 years of age, parental or legal guardian consent was obtained and patient assent was obtained. Baseline demographic and characteristics are summarised below in Table 1.

Table 1: Baseline demographics and characteristic of patients in the two treatment groups

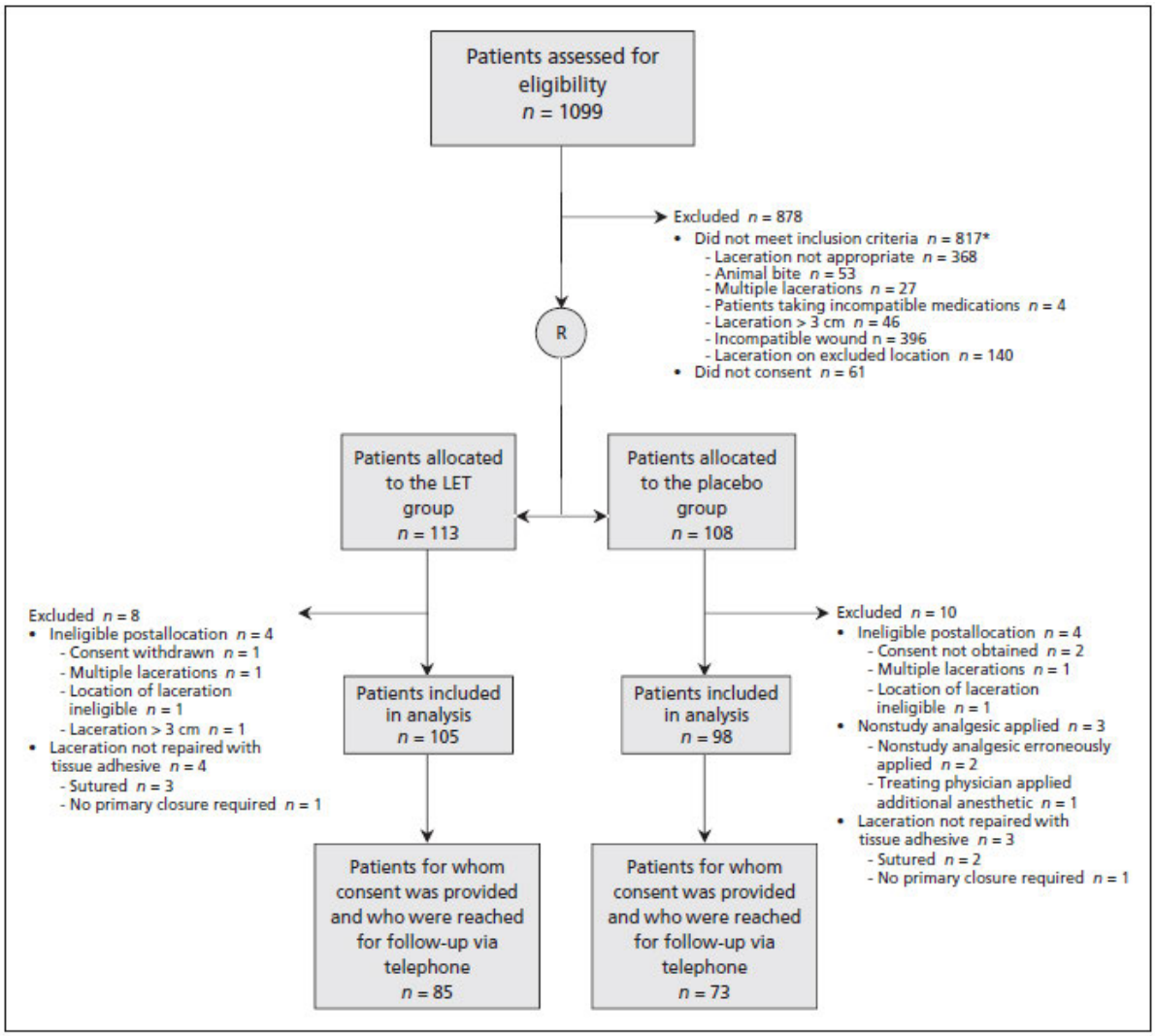
Characteristic	Study group, no. (%)*	
	Treatment *n* = 105	Placebo *n* = 98
Age, yr, mean ± SD	5.07 ± 3.94	4.21 ± 3.62
Female sex	40 (38.1)	42 (42.9)
Location of laceration		
Face	100 (95.2)	92 (94.0)
Torso	1 (0.9)	0 (0.0)
Trunk	1 (0.9)	0 (0.0)
Extremities	4 (3.8)	5 (5.1)
Other	0 (0.0)	1 (1.0)
Length of laceration, cm, mean ± SD	1.15 ± 0.60	1.31 ± 0.68
Age of laceration, hr, mean ± SD	1.93 ± 3.02	2.53 ± 7.38
Length of time LET applied before procedure, hr, mean ± SD	1.17 ± 0.40	1.21 ± 0.94

Note: LET = lidocaine–epinephrine–tetracaine, SD = standard deviation.
*Unless otherwise indicated.

Source: Harman 2013, Table 1.

Patient disposition is summarised below in Figure 1. Of the 1099 patients assessed for eligibility, 221 met the inclusion criteria and were enrolled in the study and 203 were included in the analysis of the primary outcome (105 in the LET group and 98 in the placebo group).

Figure 1: Patient disposition.



Source: Harman 2013, Figure 1.

4. Treatments

Patients were treated either with a topical LET gel or placebo gel. Nurses unaware of group assignment used tape or film dressing to affix cotton balls soaked with 3 mL of study gel to each wound. Study gel remained on wounds for a minimum of 45 minutes to ensure effectiveness. Study gel was removed by treating physicians at the time of wound repair, not longer than 120 minutes after application, as per protocol. Treating physicians repaired lacerations using *n*-butyl-2 cyanoacrylate tissue adhesive as per the usual technique.

5. Randomisation and blinding

Identical opaque envelopes containing syringes with 3 mL of LET gel or placebo gel were prepared and sealed by staff in the hospital pharmacy and stored in the ED. Envelopes were sequenced using computer-generated randomisation, coded for later identification and used by nurses in a predetermined order. The active and placebo were identical in appearance, volume, weight and odour. Nurses unaware of group assignment used tape or film dressing to affix cotton balls soaked with 3 mL of study gel to each wound.

6. Efficacy endpoints

The ***primary outcome*** was the amount of pain reported during the application of tissue adhesive using the validated 10-unit colour visual analog scale (c-VAS). Patients aged 7 years and older rated their own pain; parents or guardians of younger patients rated their children's perceived pain. Pain was also rated by patients, parents or guardians using the validated 10-point Faces Pain Scale-Revised (FPS-R), a recommended adjunct to the c-VAS for school-aged children.

The ***secondary outcomes*** at the time of wound closure included (1) physician rating of difficulty of repair on a 100-mm VAS (0 = easiest repair; 100 = most difficult repair), (2) physician rating of wound haemostasis achieved before repair (4-point Likert scale), and (3) physician prediction of active drug or placebo application. No previously validated tools for these secondary measures exist, although the same scale for difficulty of repair has been used in a previously reported study of tissue adhesives.

Two weeks after wound repair, patients were contacted by telephone and asked about unscheduled follow-up visits and their overall satisfaction.

7. Statistical methods

Based on previously published pain scores for tissue adhesive, a sample size of 115 participants in each of the study arms captured an improvement of 1 unit on the c-VAS with a p value of 0.05 and power of 80%. The study reported stated that 10% of a scale's range (e.g., 1 unit on a 10-unit scale) is the smallest change considered clinically significant in pain scales. Baseline characteristics as means and standard deviations, medians and interquartile ranges (IQRs) or frequencies and percentages, as appropriate. Scores for the treatment and placebo groups from the c-VAS and FPS-R were analysed using 2-sided Wilcoxon rank-sum tests; χ^2 tests were used for analysis of categorical variables. Relative risks (RRs) and 95% CIs of reporting pain were calculated and, where needed, Cochran–Mantel–Haenszel estimates were used to adjust for age. A generalised linear model was used to assess the effects of age (dichotomised as < 7 yr vs ≥ 7 yr) and group (active drug or placebo) on c-VAS. A χ^2 test was used to evaluate any association between dichotomised age and painful or pain-free wound closure as assessed by the FPS-R. A Bonferroni adjustment was applied to establish a more conservative cut-off for significance for multiple comparators (haemostasis; p=0.0125).

8. Efficacy – results

- ***Primary efficacy outcome:***

Children receiving LAT reported less pain than those who received placebo, based on c-VAS scores (median 0.50 [IQR: 0.25, 1.50] for treatment group vs median 1.00 [IQR: 0.38, 2.50] for placebo group; Wilcoxon rank-sum test p=0.01). Pre-treatment with LET significantly increased the proportion of pain-free procedures: 51.6% of children receiving the analgesic reported "no pain" according to the FPS-R, compared with 28.3% of those receiving placebo (RR=0.54 [95% CI: 0.37, 0.80]). This difference remained significant after controlling for age (< 7 yr vs ≥ 7 yr) (RR = 0.55 [95% CI: 0.38, 0.82]) and for level of physician training (RR=0.56 [95% CI: 0.38, 0.84). In a planned analysis, for a multinomial model of c-VAS, allocation was significant (p=0.03); categorised age and the interaction between categorised age and allocation were not significant (p=0.4 and p=0.7, respectively). The primary efficacy outcome is summarised below in Table 2.

Table 2: Pain as measured by scores on the colour Visual Analogue Scale and Faces Pain Scale — Revised for treatment and placebo groups

Pain scale	Score, median (IQR)		*p* value*
	Treatment	Placebo	
Colour Visual Analogue Scale	0.50 (0.25–1.50)	1.00 (0.38–2.50)	0.01
Faces Pain Scale — Revised	0.00 (0.00–2.00)	2.00 (0.00–4.00)	< 0.01

Note: IQR = Interquartile range.
*One-way χ^2 tests for equal proportions.

Source: Harman 2013, Table 2.

Comment:

The minimum clinically significant change reported for VAS scales is reported to be 10% of the total scale. Thus, a statistically significant difference in medians of 0.5 cm on the colour VAS does not achieve clinical relevance. The minimum clinically significant change in the FPS-R has been reported as 1 face. Thus, the difference between the treatment groups in the FPS-R is clinically relevant and statistically significant

- ***Secondary efficacy outcomes:***

- Physicians more frequently rated wound haemostasis as complete, no bleeding, in the LET group than in the placebo group (78.2% [n=79] vs 59.3% [n=54], p < 0.008). Partial wound haemostasis (mild oozing) occurred more frequently in the placebo group than in the LET group (30.8% [n=28] vs 18.8% [n=19], p=0.03, respectively), poor wound haemostasis (moderate oozing) occurred more frequently in the placebo group than in the LET group (8.8% [n=8] vs 3.0% [n=3], p=0.05, respectively), and continuous bleeding occurred in no patients in the LET group and 1 (1.1%) patient in the placebo group (p=0.2).

- The difference in physicians' rating of difficulty of wound repair between the 2 groups using the 100-mm VAS was not statistically significant (median = 6.50 [IQR: 2.5, 17.5] for the LET group; median = 9.00 [IQR: 4, 20] for the placebo group; Wilcoxon rank-sum test p=0.07).

- The results of a telephone survey at 2 weeks follow-up showed no association between allocation and follow-up needs (n=139, p=0.7, Fisher exact test) or families' subjective overall satisfaction with their children's wound repair (n=139, p=0.5, χ^2 test).

- Physicians correctly guessed which treatment was applied in 72.8% of patients, with LET incorrectly thought to be placebo in 10.4% of participants, and placebo thought to be LET in 16.8% of participants. Using Wilcoxon tests no differences between c-VAS scores for patients in the treatment and control groups within those guessed to be in the control group (p=0.7) and those guessed to be in the treatment group (p=0.9).

9. Safety – results

No adverse effects were observed or reported when assessed by physicians in the ED or during telephone survey at 2 weeks' follow-up.

10. Evaluator's comments – strengths and limitations

This was a reasonable quality randomised, placebo (gel) controlled, double-blind clinical trial in children and adolescents with short (< 3 cm in length) skin lacerations suitable for repair with tissue adhesive. The concentrations of the constituents of the LAT gel were not provided in this study, but indirect evidence suggests that the LAT gel formulation are lidocaine 4%, adrenaline 1:1000 and tetracaine 0.5%. The lacerations in this study were not sutured but repaired with "skin glue", which is a less invasive procedure than suturing. The authors reported that although less painful than cutaneous sutures, tissue adhesives polymerize through an exothermic reaction that may cause a burning, painful sensation. Pain is dependent on the specific formulation of the

adhesive used and the method of application. The baseline demographic and characteristics of patients in the two treatment groups were well balanced. The lacerations in both treatment groups were predominantly on the face.

Patients in the LET group reported statistically less pain based on the c-VAS pain scale than patients in the placebo group following pre-treatment application compared to patients in the placebo group. However, the numerical difference between the two groups in favour of LET was not clinically significant. Patients in the LET group reported statistically less pain based on the FPS-R than patients in the placebo group following pre-treatment application compared to patients in the placebo group, and the difference between the two groups was considered to be clinically meaningful. The proportion of patients achieving complete haemostasis was statistically significantly greater in the LET group than in the placebo group, and the difference between the two groups is considered to be clinically meaningful.

The study report identifies the following limitations: "Physicians correctly guessed whether the analgesic or the placebo was applied 73% of the time, calling into question whether they were truly blinded to the treatment applied. Although efforts were made to construct this study as double-blinded by concealing treatment allocation from physicians, visible blanching on the skin of some patients occurs owing to the vasoconstricting effect of topically applied or locally administered epinephrine. However, all of the physicians who participated in our study completed a standardized, mandatory training module specifically instructing them not to give patients any indication concerning to which treatment arm they might have been allocated. In addition, nurses applying the intervention had no subsequent contact with the participants, and thus did not have the opportunity to see potential wound blanching. Finally, the patients themselves were unlikely to be aware of the possibility of skin blanching, and our primary outcome was patient reported".

No mention of this study report was identified in the Cochrane Review (Tayeb 2017). It is assumed that this was because skin repair used adhesive glue rather than suturing or stapling, which was a study requirement for inclusion in the Cochrane Review (Tayeb 2017).

12.1.7. Resch 1998

1. Objectives

The objective of this study was to compare the adequacy and efficacy of topical anaesthesia experienced with LET solution versus LET gel during suturing of uncomplicated lacerations on the face or scalp in children.

2. Methods

This study was a prospective, single-blinded, randomised, controlled clinical trial that enrolled a convenience sample of 200 children who presented to the ED of a university affiliated private children's hospital in Minneapolis, Minnesota, USA, from March 1995 to March 1996. Of the 200 patients, 197 patients were analysed and relevant information was missing for 3 patients: 105 patients were randomly assigned to LET solution and 92 patients were randomly assigned to LET Gel. Three patients were withdrawn from the study before the 27-gauge needle test for adequacy of anaesthesia because of patient uncooperativeness or discovery of a complicated laceration that did not meet the inclusion criteria (2 from the solution group and 1 from the gel group). This left 103 patients in the solution group and 91 in the gel group (total 194 patients). The study design and patient consent procedures were approved by the relevant institutional review board.

3. Patients

Children were eligible if they had an uncomplicated laceration of the face or scalp that could be completely covered by a sterile 2x2-inch (5x5-cm) gauze square. Informed consent was obtained from the parent or guardian and assent from children who were 7 years of age or older. Children were excluded if their laceration was complicated. Complicated lacerations involved end arteriolar circulation (ear, nasal alae) or significant injury to an underlying structure (bone, cartilage, tendon, nerve, vessel, or parotid duct). Dirty wounds, such as mammalian bites or lacerations contaminated with soil or fecal material, were also excluded. In addition, patients who had taken or received sedative medication within the last 8 hours or uncooperative patients were excluded. The two treatment groups were comparable as regards baseline demographic and other characteristics (see Table 1, below).

Table 1: Characteristics of the two treatment groups.

Variable	LET solution	LET gel
Mean SD age (y)	5.6±3.1	5.8±3.5
Sex (males/females)	67/38	65/27
LET on laceration (min)	21±3	21±2
Length of laceration (mm)*	12.0±5.9	12.7±5.9
No. of subcutaneous sutures*	1.0±1.0	1.0±1.4
No. of superficial sutures*	5.2±2.1	5.0±2.2
No. of total sutures*	6.2±3.0	6.0±3.2
Suture time (min)*	13±7	13±8

*Of the 162 patients receiving adequate anesthesia

Source: Resch 1998, Table 2.

4. Treatments

Both the LET solution and gel formulations contained lidocaine 4%, epinephrine (adrenaline) 1:1000 (0.1%) and tetracaine 0.5%.

After patient enrollment, an application nurse applied the randomised dose of study medication to the wound for 20 minutes. If the patient was randomly assigned to receive LET solution, the solution was painted into the laceration with a cotton-tipped applicator. The remainder of the

LET solution was applied to a 2x2-inch gauze pad that was held in place by the patient's guardian or secured with tape. If the patient was assigned to receive LET gel, the gel was applied to the laceration with a cotton tipped applicator and left uncovered. The solution or gel was irrigated from the wound with 20 mL of normal saline solution before the entrance of the suture personnel into the room. This was considered time 0. The suture personnel further irrigated the wound with 100 mL of dilute povidone iodine.

5. Randomisation and blinding

A computer generated random number table was used by hospital pharmacy personnel to label standard amber vials from 1 to 200. The nurse applying the study medication selected study vials in numbered sequence. If the study vial was empty, 3 mL of stock LET solution was applied. If the study vial contained methylcellulose, 3 mL of the stock LET solution was added and stirred for 2 minutes to form gel. Each randomised dose was prepared by an application nurse immediately before its use and the study medication was left in place for 20 minutes. To ensure blinding of suture personnel, it was required that the study medication be applied by a nurse not involved in suturing.

6. Efficacy endpoints

Pain assessment was a 2-stage process that evaluated adequacy of anaesthesia before suturing and effectiveness of anaesthesia during suturing. The patient's wound was probed after LET removal and wound irrigation, but before suturing, by use of a 27-gauge needle to assess adequacy of anaesthesia. If pain was experienced, anaesthesia was considered inadequate, the time was recorded, and the laceration was infiltrated with lidocaine. If no pain was experienced, anaesthesia was considered adequate. Only if topical anaesthesia was adequate did suturing continue during which effectiveness of anaesthesia was further evaluated.

Effectiveness of anaesthesia during suturing was divided into 3 categories: complete, partial, and incomplete. This stratification was based on the time interval from removal of the anaesthetic by the application nurse to the end time of effective anaesthesia as determined by the suture personnel or the time of suture completion. The definitions of the study terms are summarised below in Table 2.

Table 2: Definitions of effectiveness of anaesthesia.

Classification	Definition
Adequacy of anesthesia	
Adequate	No painful response* is noted when the wound margin is probed with a 27-gauge needle before suturing.
Inadequate	A painful response is noted when the wound margin is probed with a 27-gauge needle before suturing.
Efficacy of Anesthesia	
Complete	Suturing is finished without supplemental lidocaine or a painful response requiring supplemental lidocaine at least 30 minutes after removal of the anesthetic from the wound.
Partial	A painful response requiring supplemental lidocaine between 15 and 30 minutes after removal of the anesthetic from the wound.
Incomplete	A painful response requiring supplemental lidocaine within 15 minutes after removal of the anesthetic from the wound.

*Painful response was considered a sudden grimace or wince, pulling away, or increase in intensity of the patient's cry that occurred simultaneously with the touch of the 27-gauge needle.

Source: Resch 1998, Table 1.

7. Statistical methods

A sample size of 100 patients in each treatment group was calculated to give 75% power to detect a difference in the proportion of complete anaesthesia from 75% in the LET solution group to 90% in the LET gel group, a difference that would be significant at an alpha of 5%. Descriptive statistics were used to characterize the study sample. Fisher's exact test was used to compare the percentage of patients in each efficacy category by group.

8. Efficacy – Results

Of the 194 patients randomised to treatment, 162 (83.5%) obtained adequate anaesthesia as determined by the 27-gauge needle test. There was no statistical difference in adequacy of anaesthesia between LET solution (87/103, 84%) and LET gel (75/91, 82%) (difference 2% [95% CI: –8%, 13%).

Effectiveness of anaesthesia (assessed in those patients who experienced adequate initial anaesthesia) during suturing was defined as complete, partial, or incomplete. Effectiveness was significantly different for the 2 formulations (p=0.007 by Fisher's exact test) largely because there were notably fewer patients with partial anaesthesia in the LET gel group compared with the LET solution group (5% vs 21%, respectively). Complete anaesthesia was recorded in a greater proportion of patients in the LET gel group than in the LET solutions group (85% [64/85] vs 76% [66/87], respectively; difference = 9% [95% CI: -3% to 22%]). However, the percentage of patients achieving incomplete anaesthesia was also greater in the LET gel group (7/75 [9%]) compared with the LET solution group (3/87 [3%]); difference = –6% [95% CI: –2% to 14%).

The efficacy results are summarised below in Table 3.

Table 3: Efficacy results

Anesthesia	LET Solution No. (%)	LET Gel No. (%)
No. enrolled	103	91
Inadequate	16 (16)	16 (18)*
Adequate	87 (84)	75 (82)
Complete	66 (76)	64 (85)*†
Partial	18 (21)	4 (5)*†
Incomplete	3 (3)	7 (9)*†

Those with inadequate anesthesia on initial assessment were injected with lidocaine and dropped from further evaluation. Those with adequate anesthesia on initial assessment were sutured and assessed as complete, partial, or incomplete (see text).
*P=.017.
†P=.007 by Fisher's exact test.

Source: Resch 1998, Table 3.

Of the 162 patients with adequate anaesthesia, data were available in all but 4 patients for the duration of anaesthesia. The mean duration of anaesthesia was the same in both groups, 21 minutes.

9. Safety – Results

No adverse effects were noted in the 194 patients during the procedure. Post-treatment follow-up was obtained for 181 of the 194 (93%) patients. Of the 13 patients who were not able to be contacted, 8 were in the LET gel group and 5 were in the LET solution group. One patient in each study arm sought medical care for a wound infection.

10. Evaluator's comments – strengths and limitations

This was a good quality prospective, single-blinded, randomised, clinical trial comparing LAT solution with LAT for topical anaesthesia for paediatric patients with lacerations of the face or scalp. No statistically significant or clinically meaningful differences were observed between the two treatment groups as regards the adequacy of initial anaesthesia. There was a statistically significant difference between the two treatment groups as regards effectiveness of anaesthesia during suturing. This difference was reported to be largely related to a decrease in the number of subjects with partial anaesthesia in the LET gel group and a concomitant increase in the

proportion of subjects with complete and incomplete anaesthesia in the LAT gel group. The study report states that "the difference in anaesthesia between treatment arms could be explained by a number of factors. First, the difference may be due to chance. Second, LET solution was painted into the wound with the remainder of the 3-mL dose applied to a 2x2-inch gauze and held in place by a guardian or secured with tape. Partial anaesthesia may have occurred more often with solution because the gauze was not held tightly against the skin after initial application. The gel, unlike the solution, tends to remain where it is placed. Inadequate placement of the gel into the wound may have contributed to the increase in number of subjects experiencing incomplete anaesthesia". The study report concludes that "LET gel is at least as effective as LET solution for effective topical anaesthesia for uncomplicated lacerations of the face and scalp in children."

The study was included in the Cochrane Review (Tayeb 2017).

12.1.8. Vandamme 2015

1. Objectives

The aim of *Vandamme 2015* was to describe the potential value of the use of LAT gel in older children and adults with simple lacerations. In addition, the study aimed to define an adult population in which LAT gel could provide an advantage compared with infiltrative anaesthesia.

2. Methods

This retrospective descriptive study was carried out in the ED of the Ghent University Hospital, Belgium, as part of a quality audit project. All ED records of patients who received LAT gel for laceration repair were reviewed. Cases were identified during a 3-month period following the initial protocol implementation. Only patients aged 8 years or older were included in the study to allow for pain self-reporting. Patients under the influence of alcohol/drugs as well as patients who had received additional sedation with nitric oxide (50% oxygen premixed) were excluded. The study was approved by the ethics committee of the Ghent University Hospital.

3. Patients

In the 3-month study period, 275 patients older than 8 years of age were sutured in the ED. In 157 cases, no LAT gel was used because of either protocol exclusion criteria at triage (in view of location, length, patient status) or being missed (in view of ED crowding). In 118 cases, LAT gel was applied. However, another 29 cases were excluded from the analysis (17 intoxicated, 8 received nitric oxide, 4 with long lacerations), retaining 89 cases for analysis. In the study population, 21 (23.6%) patients needed additional anaesthesia after needle probing or during treatment. Demographic and wound characteristics of the groups requiring additional anaesthesia or not requiring additional anaesthesia are summarised below in Table 1.

Table 1: Patient characteristics of both groups

	n (%)		
	Additional anesthesia needed (*n* = 21) (23.9%)	No additional anesthesia needed (*n* = 67) (76.1%)	*P*-value
Age [median (IQR)] (years)	36 (25–50)	30 (20–47)	0.275
Sex			
Male	14 (66.7)	46 (67.6)	0.933
Length [median (IQR)] (cm)	2.5 (2.0–4.5)	1.75 (1.0–3.0)	0.003
Length categories			0.008
Short laceration (0–2 cm)	8 (38.1)	46 (67.6)	
Intermediate-length laceration (2.1–4 cm)	8 (38.1)	19 (27.9)	
Long laceration (4.1–7 cm)	5 (23.8)	3 (4.4)	
Location of the laceration			0.041
Head	4 (19)	30 (44.1)	
Extremities/trunk	10 (47.6)	15 (22.1)	
Fingers/toes	7 (33.3)	23 (33.8)	
Treatment			0.049
Sutures	21 (100)	52 (76.5)	
Staples	0 (0)	8 (11.8)	
Others	0 (0)	8 (11.8)	
VAS needle probing [median (IQR)] (cm)	2.0 (2.0–4.0)	1.0 (0.0–3.0)	0.008
Time between application and needle probing [median (IQR)] (min)	36 (33–47)	38 (32–45)	0.582

The *P* values are calculated using the χ^2-test or the Mann–Whitney *U*-test.
IQR, interquartile range; VAS, visual analogue scale.

Source: Vandamme 2015, Table 1. Note: The analysis included 89 patients but Table 1 included data on only 88 patients.

All patients in the analysis population were adults, with mean age of 36 years (range: 25, 50 years) in the additional anaesthesia needed group and 30 years (range: 20, 47 years) in the no additional anaesthesia needed group. In both groups, the length of the lacerations were ≤ 7 cm, and the majority of lacerations were on the extremities/trunk and fingers/toes in the additional anaesthesia needed group and the head in the no additional anaesthesia needed group. Sutures were used to repair the laceration in all patients in the additional anaesthesia needed group and 75% of patients in the no additional anaesthesia needed group, with remainder of repairs in this group being split between staples and others. The median pain score assessed by VAS after needle probing was 2.0 (IQR: 2.0, 4.0) in the additional anaesthesia needed group and 1.0 (IQR: 0.0, 3.0) in the no additional anaesthesia needed group, with median time being between application of anaesthesia and needle probing being similar in the two groups (36 and 38 minutes, respectively).

4. Treatments

LAT gel was prepared by the Ghent University Hospital pharmacy in sterile 3 mL syringes. The active ingredients of LAT gel were lidocaine 4%, adrenaline 1:1000 (0.1%) and tetracaine 0.5%. Administration of LAT gel in the ED accorded with a written protocol for traumatic lesions that would probably require sutures or staples. Contraindications for the application of the gel were wounds located on the nose, ear, genitalia, and mucous membranes, and allergy to one of the constituents of the gel. If the triage nurse suspected the involvement of tendons and/or nerves the protocol was not applicable. In addition, the protocol was not applicable if the length of the laceration was > 7 cm. LAT gel was applied at triage by the triage nurse. The dose of the gel was 0.5 ml/cm, up to a maximum of 1 ml/kg. The gel was applied directly into the wound using non-absorbent gauze and was covered with an adherent dressing. The gel remained on the wound for 30 minutes. Needle probing was then performed with a 23-gauge needle to check whether the wound was anaesthetized sufficiently to enable repair. If so, the physician started wound preparation and wound closure. If the wound was not sufficiently anaesthetized, additional anaesthesia (lidocaine hydrochloride 2% infiltration) was administered. A VAS pain score was obtained during needle probing.

5. Randomisation and blinding

Randomisation and blinding were not applicable as the study was retrospective and descriptive, with all patients being treated with topical LAT gel for anaesthesia.

6. Statistical methods

Each variable was assessed on the basis of a Shapiro–Wilk test and a quantile-quantile (QQ) plot to check whether the values are normally distributed. As no normally distributed variables were found, only nonparametric tests were used. Continuous variables were reported as medians and interquartile ranges (IQRs) (Q1–Q3). Categorical data were reported as frequency of occurrence. To compare categorical variables, the χ^2 test was used. Continuous and categorical variables were compared using the nonparametric Mann–Whitney U-test or the Kruskal–Wallis test, respectively. Where informative, a 95% confidence interval (CI) was provided for the difference between medians and for the differences between proportions. Sample size calculations were no applicable for this study.

7. Efficacy endpoints

Pain was assessed during needle probing measured with pain being scored on a 10 cm visual analog scale (VAS), ranging from none to worst. The need for additional anaesthesia was considered to be the primary measure of LAT gel efficacy and was used as the primary outcome.

Lacerations were categorised by length: short-length laceration (0–2 cm), intermediate-length laceration (2.1–4 cm), and long-length laceration (4.1–7 cm); and by location: head, extremities/trunk, and fingers/toes.

8. Efficacy results

Of the 89 patients included in the analysis who had LAT gel applied at triage, 21 (23.6%) needed additional anaesthesia after needle probing or during treatment compared with 68 (76.4%) patients who did not require additional anaesthesia [results from Figure 1 of the report].

Lacerations located on the head need significantly less additional anaesthesia than lacerations located on the extremities, trunk, fingers, or toes (95% CI for the difference between proportions 1% to 34.8%). Lacerations of the head required no additional anaesthesia in 88.24% of cases (i.e., 30 cases) and additional anaesthesia in 11.76% of cases (i.e., 4 cases); lacerations of the extremities/trunk required no additional anaesthesia in 60.00% of cases (i.e., 15 cases) and additional anaesthesia in 40.00% of cases (i.e., 10 cases); and lacerations of the fingers/toes required no additional anaesthesia in 76.67% of cases (i.e., 23 cases) and additional anaesthesia in 23.33% of cases (i.e., 7 cases).

A significant difference was observed in VAS pain scores at needle probing between the different locations, with median VAS values (cm) being 0 (IQR: 0.0, 2.0) in the head, 2.0 (IQR: 0.5, 3.0) in the extremities/trunk, and 3.0 (IQR: 2.0, 4.0) in the fingers/toes; Kruskal–Wallis test, p=0.001.

The length of the lacerations was also associated with the need for additional anaesthesia (95% CI for the difference between medians 0.5 to 2; p< 0.005). Short lacerations (0 to 2.0 cm) needed no additional anaesthesia in 85.19% of patients (i.e., 46/54 cases) compared with additional anaesthesia being needed in 14.81% of patients (i.e., 8/54 cases); intermediate length lacerations (2.1 to 4 cm) needed no additional anaesthesia in 70.37% of patients (i.e., 19/27 cases) compared with additional anaesthesia being needed in 29.63% of patients (i.e., 8/27 cases); and long length lacerations (4.1 to 7.0 cm) needed no additional anaesthesia in 37.5% of patients (i.e., 3/8 cases) compared with additional anaesthesia being needed in 62.5% of patients (i.e., 5/8 cases).

9. Safety – results

In the ED of the Ghent University Hospital, the maximum dosage for LAT gel is set at 1 ml/kg and 0.5 ml/cm laceration. No complications were reported in the study population. However, as there was no follow-up, no information was available on the wound infection rate or the cosmetic outcome.

10. Evaluator's comments – strengths and limitations

The study reported in Vandamme 2015 formed part of a quality audit undertaken to assess the ED unit in a Belgian hospital. The focus of this retrospective observational study was on the need for additional anaesthesia in all patients treated in the ED administered Laceraine prior to repair of superficial skin wounds. All patients in the analysis population were adults. Additional anaesthesia was required by 21 (23.6%) of the 89 patients in the analysis population treated with Laceraine. Sutures were used to repair the laceration in all patients in the additional anaesthesia needed group and 75% of patients in the no additional anaesthesia needed group, with remainder of repairs in this group being split between staples and others.

In both groups, the length of the lacerations were ≤ 7 cm, and the majority of lacerations were on the extremities/trunk and fingers/toes in the additional anaesthesia needed group and the head in the no additional anaesthesia needed group. Lacerations on the head required less additional anaesthesia than those on the trunk, extremities, finger or toes, and there was a significant difference in VAS pain scores at needle probing between different locations. The length of lacerations was also associated with the need for additional anaesthetic with short lacerations requiring less anaesthetic compared with intermediate and long lacerations and intermediate requiring less compared with long lacerations. It was noted that only lacerations treated with sutures needed additional anaesthetic. No complications were reported in the study population. The study report concluded that LAT gel is a valuable alternative to infiltrative anaesthesia for

laceration repair. It seems to be specifically suitable for short lacerations (<4 cm), lacerations located on the head, and simple finger lacerations.

The limitations of this study arise from its design as a retrospective, uncontrolled, observational study in which all patients meeting the eligibility criteria had received Laceraine. There were no data on the initial VAS pain score prior to application of Laceraine, time taken to achieve anaesthesia or duration of anaesthesia. There was no follow-up in the study, which results in no data about the incidence of wound infection or wound dehiscence.

The study was not included in the Cochrane Review (Tayeb 2017). The study did not meet the requirements for this review as it was not a randomised controlled study and did not comprehensively assess efficacy.

12.1.9. White 2004

1. Objectives

Objectives, to determine the effectiveness of LAT in providing adequate anaesthesia for the repair of finger lacerations and to monitor the risk of digital ischaemia following application of LAT gel to finger lacerations.

2. Methods

The study was a prospective case series conducted in an academic paediatric ED in the USA with an annual census of 44,000 patients. Children aged 5 to 18 years with a simple finger laceration requiring repair were eligible for enrollment. The institutional Research and Publications Committee/Human Rights Review Board approved the study. Informed consent was obtained for all enrolled patients, as well as assent from children 7 years or older.

3. Patients

Children aged 5 to 18 years with a finger laceration requiring repair were eligible for enrollment. Inclusion criteria included superficial finger laceration less than or equal to 3 cm in length, laceration less than 8 hours old, developmentally appropriate child, and telephone follow-up availability. Exclusion criteria included allergy to LAT gel, triple antibiotic ointment, or phentolamine; involvement of the joint space, tendons, or nerves; association with a fracture, nail-bed injury, or animal/human bite; and inability to obtain a pain score.

A total of 68 patients were enrolled in the study. One child, who had no complications, was excluded from analysis because the laceration length was subsequently found to be > 3 cm, leaving 67 patients eligible for analysis. The mean age was 11.9 years. Of all patients, 65.7% (44/67) were male and 68.7% (46/67) were white. Of all lacerations, 52.2 % (35/67) were located on the dorsal surface, and 47.8% (32/67) on the ventral surface of the finger.

4. Treatments

Enrolled patients had LAT gel applied to their wound, with a standardised maximum volume of 1.5 mL. Occlusive dressing was applied over the LAT gel to hold it in place for a 45-minute period. This time was chosen based on the recommended application time of 20 to 30 minutes for facial and scalp lacerations, and extrapolated to 45 minutes based on its decreased effectiveness seen in the extremity. The LAT gel was prepared by the pharmacy as a mixture of 4% lidocaine, 0.5% tetracaine, and 1:2000 (0.05%) epinephrine with methylcellulose and preservatives.

Adequacy of anaesthesia was assessed with a 30-gauge needle after removal of LAT gel by the treating physician, followed by an examination of the digit for signs of ischaemia. Digital ischaemia was defined as a capillary refill time of > 3 seconds or a white/pale distal digit. Patients who reported a sharp sensation when tested with the 30-gauge needle were considered LAT failures. These patients evaluated their pain on a validated 0 to 10, vertical numeric visual analog scale (VAS), where 0 is marked ‘‘no pain,’’ 5 is marked ‘‘moderate pain,’’ and 10 is marked ‘‘worst pain.’’ Additional infiltrative anaesthesia (either local infiltration or digital block at the discretion of the treating physician) was provided for all LAT failures.

Patients who reported no initial sharp sensation began wound repair. All wounds were irrigated with 100 mL/cm of normal saline solution and repaired with non-absorbable suture by the treating physician. Patients who reported any sharp sensation during laceration repair were also considered LAT failures, evaluated their pain on the VAS, and received additional anaesthesia as described above. Patients who completed wound repair without reporting a sharp sensation were LAT successes and were asked to rate the overall discomfort of their procedure on the VAS. Patients and their parents were then asked if they would prefer the use of LAT gel again for subsequent lacerations of the finger. Persistent ischaemia at 60 minutes was to be treated with local infiltration of 1 mg of phentolamine.

All patients had triple antibiotic ointment applied to their wound. The choice of dressing and splinting was at the discretion of the treating physician. Patients were contacted by telephone within 3 to 5 days following discharge from the ED to assess complications (ischaemia and infection).

5. Randomisation and blinding

Not applicable as the study was a prospective case series of children treated with LAT.

6. Efficacy endpoints

The primary outcome measure was LAT success/failure. Failure was defined as any sharp sensation reported by the patient either before or during suturing. Additionally, patient and parental satisfaction with the LAT treatment was assessed by a single question.

7. Statistical methods

The proportion of patients successfully anaesthetised and the proportion of patients experiencing digital ischaemia with 95% CIs were calculated. Proportion differences and mean differences with 95% CI were given for outcome measures. Categorical data were reported as frequency and analysed using χ^2 analysis. Continuous and ordinal data were compared using the unpaired Student t-test.

An initial sample size of 96 was based on the number of patients needed to estimate a 95% CI for an expected proportion of 0.50 (±0.10) patients having adequate anaesthesia with LAT gel. Interim analysis after 68 patients revealed a confidence interval width of ± 0.12, compared to the planned ± 0.10 with 96 patients. Given the minimal clinical difference between 0.12 and 0.10, the study was concluded at 68 patients.

8. Efficacy – results

The overall success rate for LAT gel on finger lacerations was 36 out of 67 patients (53.7% [95% CI: 41.1% to 66.0%]). The mean discomfort of the procedure for LAT successes was 2.7 as measured on the VAS. LAT failures reported a mean VAS pain score of 6.7, taken at the time they reported a sharp sensation. The success rate for dorsal surface lacerations was reported in 24 out of 35 patients (68.6% [95% CI: 50.7% to 83.1%]), while the success rate for ventral surface lacerations was reported in 12 out of 32 patients (37.5% [95% CI: 21.1% to 56.3%; 12/32]). The difference in success rates was statistically significant between dorsal and ventral surface lacerations (difference = 31.1% [95% CI, 8.3% to 53.8%]).

There was no difference in mean age between the LAT success group (11.9 years) and the LAT failure group (11.8 years) (difference = 0.10 [95% CI: 1.74 to 1.91]). There was no difference in the success rates between White and Black patients (difference = 16.3% [95% CI: 12.5% to 45.2%]). There was no difference in success rates between male and female patients (difference = 10.9% (95% CI: -14.0% to 35.7%). No signs of digital ischaemia were found in the 67 cases during the ED visit (0% [95% CI: 0.0% to 5.4%]).

Following wound repair, parents and patients were asked if they would prefer the use of LAT gel again for simple finger lacerations. In the success group, 93.9% of parents and 94.3% of patients would use LAT again, while in the LAT failure group, 44.4% of parents and 50.0% of patients would use LAT again.

9. Safety – results

Ninety-three percent (62/67) of all patients enrolled were followed up with a phone call 3 to 5 days following laceration repair. There were no reported cases of ischaemia or infection.

10. Evaluator's comments – strengths and limitations

This was a good quality prospective "convenience" case series in which enrolled children meeting the eligibility criteria had LAT gel applied before suturing. The overall LAT success rate of 54%

reported in the study is stated by the authors to be "similar to previous rates noted in studies utilizing tetracaine-adrenaline-cocaine (TAC) on extremity lacerations, reporting successful anaesthesia in 43% to 55% of patients". Of note, no cases of digital ischaemia were reported in this study despite the LAT gel containing adrenaline (1:2000). Nearly 94% of both patients and parents in the success group reported that they would use LAT gel again.

The study authors noted that the small sample size (i.e., 67 patients) may compromise adequate detection of rare adverse effects and that the convenience sample may have introduced some selection bias. The authors noted that the 95% CI for the risk of digital ischaemia can only place the risk at 5.4% of less, but the authors believe "that the easily reversible nature of any digital ischemia should allow for the use of LAT with appropriate training in the use of phentolamine. Larger studies are needed to further delineate the risk of ischemia". However, despite the author's statement regarding the "ease" of reversibility of digital ischaemia it is considered that the risk is best avoided by contraindicating the use of Laceraine for repair of digital lacerations. This is reflected in the SCHN guidelines for application of Laceraine for wound anaesthesia which contraindicate the use of the product for the repair of lacerations on the digits.

The study was specifically excluded from the Cochrane Review (Tayeb 2017) on the grounds that it was not a randomised controlled trial and all participants received LAT gel.

12.1.10. Ernst 1997

1. Objectives

The objective of the study was to compare LAT gel with injectable buffered lidocaine combined with epinephrine regarding pain of application or injection and anaesthesia effectiveness.

2. Methods

The study was a randomised, prospective, unblinded, comparison trial undertaken in an urban ED in the USA. Patients were eligible if they were aged *5* years or older with simple linear lacerations 1.5 cm to 10 cm long of the extremities, face or scalp. Data were analysed for 66 patients, including 33 randomised to LAT gel and 33 to injectable buffered lidocaine with epinephrine. The study was approved by the relevant institutional review board.

3. Patients

The data were analysed after 66 patients were entered in the study, including 13 children aged 5 to 17 years. Thirty-three patients received LAT gel and 33 received injectable buffered lidocaine with epinephrine. Patients were eligible if they were aged *5* years or older with simple linear lacerations 1.5 cm to 10 cm long. Patients were excluded if they were allergic to amides or esters; if there was suspected alcohol or drug use, altered mental status, pregnancy, or glaucoma; if they did not wish to participate in the study; if the location of the laceration involved possible vascular compromise; or if the wound was more than 8 hours old.

There were differences between the groups as regards sex and amount of local anaesthesia used: there were statistically fewer females in the LAT gel group (p=0.027), and a greater volume of local anaesthetic was used in the injectable buffered lidocaine group (p < 0.001). The mean age, length of lacerations, and location of lacerations were balanced for the LAT gel and injectable lidocaine groups. The demographics of the two treatment groups are summarised below in Table 1.

Table 1: Characteristics of the two treatment groups

	LAT Gel	Injectable Lidocaine	P Value
Sex (M/F)	5/28	13/20	0.027*
Age (years)	29	30	0.36*
Length of laceration (cm)	2.3	2.5	0.87*
Initial amount of local anesthesia (cc)	1.7	4.6	0.06*
Need for more anesthesia (n)	2	0	
Location of laceration (n)			
Extremity	13	11	0.23†
Face	17	13	
Scalp	3	7	

Results are means.
*Wilcoxon rank sum test.
†χ^2 test, extremities vs face and scalp.

Source: Ernst 1997, Table 1.

4. Treatment

The topical LAT gel comprised lidocaine 4%, epinephrine 1:2000 (0.05%) and tetracaine 0.5% in a gel form (hydroxyethyl cellulose) with preservatives. The gel was prepared by a pharmacist. The total available volume of each gel application was 3 mL.

The injectable buffered lidocaine solutions were prepared by mixing l mL of 8.4% NaHCO3 with 9 mL of commercially prepared 1% lidocaine with epinephrine. The total volume available was 10 mL.

All personnel performing suturing were oriented to the protocol of slow infiltration with a 25-gauge needle. LAT gel was applied with a cotton swab in and up to l cm around the wound edge, and the gel was left in place for 10 minutes. If the patient was still sensitive to pinprick after 10 minutes, the gel remained on for another 10 minutes. If the patient was still sensitive, l% lidocaine was added. The pain of application was determined after anaesthetic was applied or injected and before suturing began. Laceration repair was performed by one of the study authors, resident physicians, or nurse practitioners oriented to the study protocol.

5. Randomisation and blinding

Patients were randomised to LAT gel or injectable lidocaine. The doses of anaesthetic were numbered 1-66 according to a computer-generated random table of numbers prepared before the study. The study was not blinded because of the obvious differences in form and application of the two local anaesthetics.

6. Efficacy endpoints

The length of the laceration, location, length of time anaesthesia lasted, amount of anaesthesia used, necessity for additional lidocaine, and treatment success or failure were recorded at the time of the procedure, along with any complications. Patients and physicians ranked the pain of injection or application and the pain of suturing (anaesthesia effectiveness) using a previously validated linear visual analog scale (VAS) so that each laceration had four associated measurements of pain. Each VAS was a horizontal line graph 10 cm long with the words "no pain" at the left end and "worst pain" at the right end. Patients were followed by telephone, return visits to the emergency department, and medical records.

7. Statistical Methods

The *a priori* analysis determined that 66 patients were needed for the study to have a power of 0.9 to detect a 1.2 cm difference in VAS readings ranging from 0 to 10 cm. The author's reported that this difference is consistent with the minimum clinically significant difference according to a previous study (Todd KH, Funk JP, 1996).

8. Efficacy – results

- The number of patients requiring further anaesthesia was two in the LAT gel group (2/33) and none (0/33) in the injectable lidocaine group (too few to apply statistical analysis). In one of the two patients in the LAT group needing further anaesthesia, the gel was not allowed to remain in place after 10 minutes of application as per protocol, and the scores for this entry were excluded from the calculations. The initial amount of anaesthetic was 1.7 mL in the LAT gel group and 4.6 mL in the injectable lidocaine group (p=0.06).

- LAT gel application was significantly less painful to apply, as assessed by the VAS, than injection of lidocaine according to both patients and physicians ($p \leq 0.001$ Wilcoxon rank sum tests): physician rating median (IQR) = 0 (0-0) for LAT gel vs 1.4 (0.45-3.45) injectable lidocaine, p=0.001; patient rating median (IQR) = 0 (0-0.15) LAT gel vs 1.2 (0.15-2.75) injectable lidocaine, p=0.001.

- For suturing (anaesthesia effectiveness), patients and physicians found no difference in pain as assessed by VAS between LAT gel and injectable lidocaine ($p \geq 0.48$, Wilcoxon rank sum

tests): physician rating median (IQR) = 0 (0-0.55) for LAT gel vs 0 (0-0.35) injectable lidocaine, p=0.83; patient rating median (IQR) = 0 (0-0.1.35) LAT gel vs 0 (0-0.6) injectable lidocaine, p=0.48.

- The number of sutures causing pain according to patients, another measure of anaesthesia effectiveness, was calculated as a percent. The mean percent of sutures causing pain was 13% in the LAT gel group and 6% in the injectable lidocaine group (p=0.28, Wilcoxon rank sum test); and the median (IQR) number of sutures causing pain was 0 (0-18) in the LAT gel group and 0 (0-0) in the injectable lidocaine group.

- Because of the difference in the number of females between the two groups, comparisons of efficacy outcomes between the sexes were undertaken. For physician and patient pain scores during suturing, sex and treatment group were not significantly different for the topical vs injectable group. There was a difference between the sexes as regards injection pain according to physicians, with females having greater pain than males (mean VAS = 2.8 vs 1.4, p=0.015). For females, LAT gel was significantly less painful to apply than buffered lidocaine was to inject. The mean scores for application for LAT gel for females was 0, and for males, 0.3.

- To determine effectiveness of LAT gel vs injectable lidocaine at extremity locations, a comparison was made for laceration scores at extremity locations vs face and scalp. Using the Wilcoxon's rank sum test, no difference was detected in physician application (p=0.49), patient application (p=0.87), or physician suturing (p=0.17) for extremity lacerations in the two groups. For patient suturing, the difference for extremities (median score 1.2; mean score 2.4) vs face and scalp (median score; mean score 0.3) was not significant (p=0.052).

9. Safety - results

Follow-up was available in 75% of the patients, with equal rates in the topical and injectable lidocaine groups. No complications or wound infections were reported.

10. Evaluator's comments – strengths and limitations

This was a good quality randomised unblinded study in children and adults comparing LAT gel with injectable lidocaine as local anaesthesia for repair of simple lacerations. The LAT gel was rated by physicians and patients to be less painful to apply than injectable lidocaine. Physicians and patients preferred LAT gel for this reason. No significant difference was found between the two formulations as regards anaesthetic effectiveness during suturing. Similarly, the number of sutures causing pain was not statistically different between the two treatment groups. The study was not blinded. However, it is considered that the use of a double-dummy technique would have been inappropriate for a study of this nature. The study is included in the Cochrane Review (Tayeb 2017). However, the authors of the review noted that the study was at "high risk of blinding bias."

12.1.11. O'Connor 2010

1. Objectives

The objectives of this study were to assess whether the introduction of LAT gel helped to reduce the number of specialist referrals by allowing the ED staff to perform the procedures in combination with non-pharmacological approaches to suturing.

2. Methods

The study was carried out in the ED of the Mid-Western Regional Hospital, Limerick, Ireland. It was a retrospective review of ED records of all children aged 14 years or less attending with lacerations or incised wounds, over an 8-month period, from 01 May 2007 to 31 January 2008. The data were collected using an Information Technology (IT) tracking system in ED. The data included patient demographics, wound site and treatment, treating physician/team, treatment with LAT and treatment requiring specialist referral and/or general anaesthetic.

3. Patients – inclusion and exclusion criteria

A total of 397 children 14 years of age or less attended with lacerations or incised wounds to the ED, during the 8-month study period. Of these, 201 (50.6%) patients presented before the introduction of LAT gel, whereas 196 (49.3%) patients presented after the introduction of LAT gel. The characteristics of the study population are shown below in Table 1. The age range of the children was from 24 days to 14 years. The demographic characteristics, wound sites, and ED treatment were well balanced between the pre-LAT and LAT groups.

Table 1: Demographic characteristics, wound sites, ED treatment and referrals.

Characteristic	Pre-LAT, *n* (%)	LAT, *n* (%)
Female	78 (39)	63 (32)
Male	123 (61)	133 (68)
Age, mean ± SD (years)	6 ± 3.5	5.8 ± 4
Wound site		
Scalp	25 (12)	31 (16)
Forehead	42 (21)	31 (16)
Face (ear, eyelid, nose, cheek)	33 (16)	39 (20)
Lip	15 (8)	21 (11)
Tongue	5 (3)	3 (1)
Chin	12 (6)	13 (7)
Fingers/hand	34 (17)	32 (16)
Upper limb	11 (5)	4 (2)
Knee	14 (7)	6 (3)
Lower limb	10 (5)	12 (6)
Trunk	0	4 (2)
ED treatment		
Sutures	69 (34)	69 (35)
Staples	10 (5)	12 (6)
Tissue adhesive	44 (22)	47 (24)
Steristrips	18 (9)	19 (10)
Dressing	10 (5)	12 (6)
Wound toilet only	11 (5)	18 (9)
Referrals		
Maxillofacial surgery	23	10
Plastic surgery	5	4
ENT	3	1
General surgery	3	2
Orthopaedic surgery	3	1
Ophthalmology	2	1

Source: O'Connor, 2010.

4. Treatment

The LAT gel was sourced from the Torbay Pharmacy Manufacturing Unit, which is part of the South Devon Healthcare NHS Trust in the UK. The constituents of LAT gel were lidocaine 4%, adrenaline 1:1000 (0.1%), and tetracaine 0.5%. The gel was not to be used on mucous membranes, digits, genitalia, ear or nose, over burns or abrasions, or where tissue was not viable. A written departmental protocol for its use was established, along with formal staff education. The protocol included indications and contraindication for use of LAT gel on wounds ≤ 5 cm in length requiring suturing.

The gel could be applied by either the nurse or doctor caring for the patient. The dose of the gel was 0.5 mL/cm of wound, up to a maximum of 2 mL in children aged < 3 years and 3 mL in children aged ≥ 3 years. Half of the gel was applied directly onto the wound and the other half was applied to non-absorbent gauze with an adherent dressing for 20 minutes. After this time, wound cleaning and suturing was to be completed within a further 20 minutes.

5. Randomisation and blinding

Not applicable. The control group in this retrospective study were patients treated prior to the introduction of the LAT gel protocol.

6. Efficacy endpoints

The efficacy criterion was the number of specialist referrals following application of LAT gel.

7. Statistical methods

The statistical methods were not described. However, standard descriptive methods were used to summarise the data and Fisher's exact test was used to assess the difference in proportion between the two groups.

8. Efficacy – results

A total of 39 (19.4%) patients were referred for specialty review pre-LAT compared with 19 (9.7%) patients in the LAT group. Of these, 31 (15.4%) patients in the pre-LAT group and 15 (7.7%) patients in the LAT group required a general anaesthetic, p=0.018, Fischer's exact test, reported Figure 1 of the text. The majority of patients in both groups were referred to maxillofacial surgeons for repair, 24 patients (11.9%) pre-LAT and 10 patients (5.1%) in the LAT group.

The most common wound sites and ED treatments were comparable in both groups, with the face/forehead being the most frequent, 75 patients (37%) pre-LAT and 70 patients (36%) after LAT introduction. The definitive treatments carried out in the ED included suturing, staples, tissue adhesive, Steristrips and dressings. Sixty-nine (34%) patients of the pre-LAT group and 69 (35%) patients of the LAT group were sutured, whereas 10 (5%) patients pre-LAT and 12 (6%) patients of the LAT group received staples. All patients who were sutured in the LAT group received application of the gel. No patients who received LAT gel required "top-up" infiltrative lidocaine analgesia.

9. Safety – results

No adverse events were noted from the use of LAT gel.

10. Evaluator's comments – strengths and limitations

This was a reasonable quality retrospective observational study comparing the requirement for specialist referral of wound repair before and after introduction of LAT gel to the ED protocol for wounds requiring suturing. There was no reference to ethics committee approval or informed consent in this study report. Total speciality referrals for wound repair were numerically lower in the LAT group than in the pre-LAT group, and the need for general anaesthesia was statistically significantly lower in the LAT group compared with the pre-LAT group. No patients who received

LAT gel required "top-up" infiltrative lidocaine analgesia and there were no adverse events noted from its use.

This was a retrospective observational study comparing pre-LAT to post-LAT for wound repair. Consequently, the study is subject to the well-known biases associated with studies of this design. The study was not included in the Cochrane Review (Tayeb 2017). The study did not meet the requirements for this review as it was not a randomised controlled study and did not assess efficacy based on pain prior to and during wound repair.

12.1.12. Lee 2013

1. Objectives

The objectives of this study were to compare LAT gel with conventional lignocaine infiltration for repair of minor lacerations, for comfort of application, efficacy, adverse effects and cost.

2. Methods

This was a prospective, randomised, controlled, clinical trial involving 40 patients who required toilet and suture for minor lacerations on the head, trunk or limb. The study enrolled patients from January 2003 through April 2003 presenting to the ED of the Singapore General Hospital (SGH), Singapore, aged ≥ 1 year up to 70 years with clean, non-bite lacerations ≤ 6 hours previously. Of the 40 included in the analysis, 23 were randomised to LAT gel and 17 were randomised to lignocaine infiltration. Approval to carry out the study at the SGH was granted by the SGH Ethics Committee. For patients aged > 1 to 18 years, consent was taken from the accompanying adult/parent.

3. Patients – inclusion and exclusion criteria

The demographic profiles of the two treatment groups are provided below in Table 1. The main difference between the two groups was mean age, with the lignocaine infiltration group being on average 10 years older than the LAT gel group.

Table 1: Demographic profile.

Variables	LAT gel (*n*=23)	Lignocaine infiltration (*n*=17)	*P* value
Age (mean, SD)	36.8 (25.7)	46.2 (23.0)	0.25
Sex (males, %)	17 (73.9)	12 (70.5)	0.73
Race (*n*, %)			
Chinese	16 (69.6)	9 (52.9)	}
Malay	3 (13.0)	4 (23.5)	}0.66
Indian	3 (13.0)	3 (17.6)	}
Eurasians	1 (4.4)	1 (5.8)	}

Source: Lee 2013, Table 1.

The characteristics of the wounds in the two treatment groups are summarised below in Table 2. The characteristics of the wounds in the two treatment groups are generally comparable, with the mean length of the wounds in both groups being ≤ 3.5 cm. The majority of wounds in both the treatment groups were located on the head.

Table 2: Characteristics of wounds.

Variables	LAT gel (*n*=23)	Lignocaine infiltration (*n*=17)	*P* value
Length of wound/cm -mean (SE)	3.1 (0.31)	3.5 (0.36)	0.45
Depth of wound/cm -mean (SE)	0.5 (0.07)	0.7 (0.08)	0.21
Location of wound (*n*, %)			
Head	17 (74.0)	11 (64.7)	}
Trunk	0	0	} 0.29
Limb	6 (26.0)	6 (35.3)	}

Source: Lee 2013, Table 2.

4. Treatments

The LAT formulation use in the ED of the SGH is lignocaine base (4%), racemic adrenaline (epinephrine) HCl (0.182%) and tetracaine HCl (0.569%). The gel was pre-prepared in a 5 mL syringe. The lidocaine control for infiltration was a 1% solution.

The clinician in charge administered the lignocaine infiltration to patients randomised to this group prior to suturing. A trained nurse applied the LAT gel prior to suturing to patients randomised to this group. The LAT gel was squirted into and around the laceration with a syringe tip. Mucous membranes were avoided. The wound was then covered with a sterile piece of gauze and taped down with micropore. The gel was allowed to remain on the wound for 20 minutes. Once anaesthesia was achieved by either lignocaine infiltration or application of LAT gel, the wound was cleaned thoroughly to remove any dirt or foreign body and the laceration was then sutured. The supplies were discarded after use.

5. Randomisation and blinding

Eligible patients were assigned to the two treatment groups using sealed envelopes. The study was not blinded.

6. Efficacy endpoints

The pain of administering the anaesthetic was scored on a 100 mm visual analog scale (VAS) ranging from “no pain” (left end) to “most marked pain” (right end). Pain of administration was also scored in children aged 10 years and below by using the same scale but with faces drawn to describe facial expressions of pain (no pain to excruciating pain). The efficacy of anaesthesia was assessed by the practitioner using a 27-gauge needle and the presence of blanching was also noted for LAT gel applications. Scoring of pain was done by the patients themselves if they were above 10 years or by the parents and the clinician if less than 10 years. Observers based pain scores on the pain experienced as the needle pierced the patients' skin to measure the actual anaesthetic performance separated from the patient’s response to fear and distress. The number of sutures needed to stitch the laceration were recorded. After the procedure, the patients were given the usual wound care advice and told to return after 7 days for review. The wound was reviewed for infection, dehiscence, erythema, redness and loss of stitches. In the event of any complication mentioned above, patient was told to return another 7 days later for further review.

7. Statistical methods

The sample size estimation before recruitment was 46, with 23 in each treatment group. These criteria were not met due to the disruption of the study by the severe acute respiratory syndrome (SARS) outbreak. Therefore, 40 patients were recruited, 23 to the LAT gel group and 17 to the lignocaine group.

For continuous data, Student's *t* test was used if the data were normally distributed. Otherwise, the Mann-Whitney *U* test was used. Fisher’s exact test was used to assess differences between the 2 groups for qualitative data (e.g., sex, race, wound contamination). Multivariate logistic regression was used to adjust for confounding variables such as age, sex and race. The analysis was based on an equivalence test of means using two one-sided tests on data with sample sizes of 23 in both groups. This achieved 80% power at a 5% significance level when the true difference between the means was 0.00, the standard deviation was 2.50, and the equivalence limits were –2.20 and 2.20.

8. Efficacy – results

Of the 40 patients included in the study, only 1 patient was < 10 years of age and this 7 year old could do the pain scoring himself. Therefore, a separate analysis of the pain data in paediatric patients was not required. The outcomes are summarised below in Table 3. There was no difference in the efficacy of the LAT gel or lignocaine infiltration before suturing ($p < 0.87$). Pain during administration of the anaesthetic was statistically significantly lower in the LAT group than in the lignocaine infiltration group ($p < 0.01$). The author’s state that a difference of ≥ 2.0 cm in the VAS between the two groups is clinically significant. Patients usually reported a slight smarting sensation when LAT gel was applied. There was no failure of anaesthetic efficacy for

the LAT gel group during the process of suturing. Hence there was no need for LAT gel patients to switch to lignocaine administration midway during the procedure.

Table 3: Efficacy outcomes.

Variables	LAT gel	Lignocaine infiltration	*P* value
Efficacy	*n*=20	*n*=16	308.31±44.57
- Pain score by patient (mean±SE)	2.5 (0.52)	2.6 (0.58)	0.87
Pain during application	*n*=22	*n*=16	<0.01
Pain score by patient (mean±SE)	1.5 (0.40)	3.5 (0.46)	

Pain profile of patients with efficacy of LAT gel vs. LI based on visual analog scoring.

Source: Lee 2013, Table 3.

9. Safety – results

Complications included wound infection, wound dehiscence and loss of stitches. There was no significant difference in the rate of complications between the two groups (see Table 4, below). As the incidence rate for wound dehiscence and stitches lost was nil in the lignocaine infiltration group, logistic regression was not done.

Table 4: Complications

Variables	LAT gel (*n*=25)	Lignocaine infiltration (*n*=14)	*P* value
Wound infection	5 (20)	2 (14.3)	0.66
Wound dehiscence	1 (4)	0	0.45
Stitches lost	1 (4)	0	0.46

Source: Lee 2013, Table 4.

10. Evaluator's comments – strengths and limitations

This was a good quality prospective, randomised, unblinded study in children and adults comparing LAT gel with conventional lignocaine infiltration for repair of minor lacerations. The doses of LAT gel and infiltrated lignocaine used in the two treatment groups were not reported. There was no significant difference in the efficacy of LAT gel vs lignocaine infiltration based on pain scores assessed by VAS using needle probing. However, improvement in patient comfort for the LAT group was significant during suturing compared with the lignocaine infiltration group based on pain scores measure by a VAS. Patients usually reported a slight smarting sensation when lignocaine gel was applied. Complications included wound infection, wound dehiscence and loss of stitches. There was no significant difference in the rate of complications between the two groups. The study was not blinded. However, it is considered that the use of a double-dummy technique would have been inappropriate for a study of this nature. The study is included in the Cochrane Review (Tayeb 2017). However, the authors of the review noted that the study was at "high risk of blinding bias."

12.1.13. Siembieda 2022

1. Objectives

The objective of this study was to determine if 3 applications of LET 10 minutes apart (triple LET) result in lower pain scores with suturing than one application for 30 minutes (single LET).

2. Methods

The study was a randomised, single-blind, clinical trial of a convenience sample of children undergoing laceration repair, comparing pain scores on first suture placement between the intervention group (3 applications of LET 10 minutes apart [triple LET]) and the control group (1 application of LET for 30 minutes [single LET]). The study used a standard LET gel formulation (lidocaine [4%], epinephrine [0.1%], and tetracaine [0.5%])

Enrollment was by convenience sampling undertaken at two paediatric EDs in the USA (Harbor-UCLA Medical and Children's Hospital of Orange County). Informed consent was obtained by a study investigator.

3. Patients

The study included patients with simple (≤ 3 cm) lacerations aged 7 to 17 years, for whom the clinician provider planned to close the laceration using simple interrupted sutures. Exclusions were patients with lacerations involving the hands, feet, genitals, tongue, mucus membranes, nose, or ears, or occurring over joints, as LET is either relatively contraindicated or known to be less effective in these areas. Developmentally delayed patients or patients with a disability preventing them from giving a reliable pain score were excluded, as were patients whose primary language was neither English nor Spanish, and patients who required procedural sedation, or anxiolytic treatment with intranasal or oral midazolam. Receipt of oral analgesic was not a reason for exclusion.

A total of 48 patients were enrolled, 21 in the single LET group and 27 in the triple LET group. The demographic characteristics of the two treatment groups were well balanced. The demographic characteristics of the two populations are summarised below in Table 1.

TABLE 1. Demographic Data

Characteristic	Overall	Single LET Group	Triple LET Group
Age, mean (SD), y	10.5 (2.8)	10.7 (3.1)	10.3 (2.6)
Sex, male, %	81%	76%	85%
Ethnicity, %			
Hispanic	75	67	81
White	8	10	7
Black	4	5	4
Asian/PI	4	5	4
Other	8	14	4
Premedication, %			
None	96	100	93
Ibuprofen	2	0	4
Acetaminophen	2	0	4
Laceration location			
Face/Scalp	79	86	74
Arm	4	0	7
Leg	17	14	19
Laceration length, mean (SD), cm	1.7 (0.7)	1.8 (0.8)	1.7 (0.7)
No. sutures placed, %			
1–2	17	15	18
3–4	47	55	41
5–6	19	5	30
>6	17	25	11

Source: Siembieda 2022, Table 1.

4. Treatment

Patients were randomised to single LET or triple LET. The investigator worked with the patient's nurse to apply either 3 mL of LET once for 30 minutes (for subjects assigned to the control group "single LET") or 3 mL of LET every 10 minutes for a total of 3 applications (for subjects assigned to the intervention group "triple LET"). The clinician provider was not informed of the study group assignment. The clinician provider began suturing within 15 minutes of completion of the 30-minute LET application, and study investigators ensured that this occurred in all cases. A nurse other than the patient's primary care nurse was asked to obtain a pain scale rating from the patient immediately after the first suture was placed or attempted to be placed. This nurse was blinded to study group and used a visual analog scale (VAS) and a standardised script for obtaining the pain rating. At this point, the study procedures regarding anaesthetic were complete, and the decision to use any additional anaesthetic infiltration was left to the clinician provider suturing the laceration. After completion of the laceration repair, the parent and clinician provider were surveyed regarding their satisfaction with the procedure.

5. Randomisation and blinding

Randomisation was by sealed sequential randomisation envelopes opened by the study investigator. The clinician provider was not informed of the study group assignment and was instructed to being begin suturing within 15 minutes of completion of the 30-minute LET application. The nurse obtaining the patient's pain rating using the VAS was blinded to the study group. The patient and patient's nurse were not blinded to group assignment.

6. Efficacy endpoints

The *primary outcome* was the difference in VAS pain scores between the triple and single LET groups. As mentioned above, a nurse other than the patient's primary care nurse was asked to obtain a pain scale rating from the patient immediately after the first suture was placed or attempted to be placed. This nurse was blinded to study group and used the VAS and a standardised script for obtaining the pain rating. The VAS is a 100-mm line with the anchor "no pain" on one end and "pain as bad as it could possibly be" on the other end. The patient was asked to mark a pain rating along the 100-mm VAS line with a pen. The VAS is a well-validated commonly used pain scale, and nurses were familiar with its use. The *secondary outcomes* included the need for additional infiltrated local anaesthetic and provider and parent satisfaction.

7. Statistical methods

The sample size needed to detect a 20-mm difference between the 2 groups, with an SD of 20 mm, a power of 0.8, and an α of 0.05, using a 2-tailed t-test was 17 per group, for a total of 34 subjects. Although the author's stated that a difference of 13 mm on a 100-mm VAS would represent a minimum clinically significant difference (based on published data), "a priori" the authors selected a difference of 20 mm (which would represent a "lot less pain") as this difference would warrant the added cost and nursing work of using triple LET. Because of plans to use a non-parametric statistical test, an additional 20% was added to the patient population (i.e., at least 42 subjects, 21 per group). Descriptive data were reported as proportions and medians. The non-parametric Wilcoxon rank sum test was used to compare the pain scores between intervention and control groups.

8. Efficacy results

The overall mean VAS score was 16 (SD=21; range, 0–95). The mean VAS score for single LET patients was 16 (SD=17; range, 0–48), and that for triple LET patients was 16 (SD=24; range, 0–95). The Wilcoxon rank sum test did not find a statistically significant difference between the 2 groups (2-sided p=0.48; difference = 0.37 [95% CI: −11.9 to 12.6). Pain scores did not differ significantly by patient sex or location of laceration, and there was no significant correlation

between pain scores and patient age or the degree of blanching around the wound noted after LET application.

Overall, 9 (19%) patients required additional anaesthesia with infiltrated lidocaine. There was no significant difference between single LET (4 of 21 [19%]) and triple LET (5 of 27 [19%]) in requirement for additional anaesthesia.

Seventy-four percent (74%) of providers and 83% of parents were very or extremely satisfied with LET. By treatment groups, 75% (15 of 20) of providers were very or extremely satisfied with single LET versus 71% (17 of 24) with triple LET, and 95% (20 of 21) of parents were very or extremely satisfied with single LET versus 74% (20 of 27) with triple LET. None of these differences were reported to be statistically significant.

9. Safety

No reference to adverse events could be identified in the study report.

10. Evaluator's comments – strengths and limitations

This was a good quality, randomised, single-blind (clinician suturer blinded), comparator, interventional study. There were no clinically meaningful differences in anaesthesia between LET single and LET triple dose administration reported by patients immediately after the first suture was placed or attempted to be placed. There was no numerical difference in the proportion of patients in the two treatment groups requiring additional anaesthesia. The authors report that "for pediatric laceration suturing, applying topical LET every 10 minutes for 3 applications was not superior in anaesthetic efficacy to applying it once for 30 minutes."

The study report identified several limitations including: unable to blind the patient or nurse caring for the patient; wide age range of the study population (7 to 17 years) all able to give self-reported VAS pain scores, therefore, results not applicable to children < 7 years; the majority of lacerations were on the face/scalp that "may be very amenable to topical local anaesthetics" and the results may not be applicable to other sites; and high pain ratings provided by some patients may have been confounded by patient anxiety.

13. Attachments: additional evaluation material

13.1. Attachment 1 – The Sydney Children's Hospital Network

LACERAINE® TOPICAL WOUND ANAESTHETIC: APPLICATION - ED

PROCEDURE

DOCUMENT SUMMARY/KEY POINTS

- Laceraine® wound anaesthetic is indicated for **topical** application to superficial wounds and lacerations to provide localised surface anaesthesia and reduce bleeding.
- A focused history and wound assessment must be performed prior to prescribing by accredited Registered Nurses (RN), Medical Officers or Nurse Practitioners.
- Laceraine® may be prescribed under a Standing Order as a single dose by accredited RN's
- Laceraine® may be applied by Medical Officers and ED Registered Nurses who have been trained in the application technique.
- Laceraine Gel is applied directly to the wound surface and retained with an occlusive dressing.

CHANGE SUMMARY

- Updated prescribing information and reduced dosing limits for Gel formulation.
- Use of Laceraine® soaked cotton wool is not required when using the Gel formulation.
- **12/04/21:** Minor review. References to Laceraine solution deleted as solution formulation is no longer available. Revised application technique. References to application of soaked cotton wool removed. Packaging and storage amended: refrigeration not required.
- **30/04/21:** Minor review. Strength amended to correspond to the manufacturer's product information, see pg 3.

This document reflects what is currently regarded as safe practice. However, as in any clinical situation, there may be factors which cannot be covered by a single set of guidelines. This document does not replace the need for the application of clinical judgement to each individual presentation.

Approved by:	SCHN Policy, Procedure and Guideline Committee	
Date Effective:	1st January 2021	Review Period: 3 years
Team Leader:	Nurse Practitioner	Area/Dept: Emergency Department SCH

Date of Publishing: 30 April 2021 8:48 AM Date of Printing: 3 January 2023 Page 1 of 7

K:\CHW P&P\ePolicy\Apr 21\Laceraine Topical Wound Anaesthetic Application - ED.docx

This Policy/Procedure may be varied, withdrawn or replaced at any time. Compliance with this Policy/Procedure is mandatory.

READ ACKNOWLEDGEMENT

Training

- Laceraine® may be applied by ED Registered Nurses who have been trained in the application technique under a Standing Order.

Acknowledgement

- All SCHN Emergency Department clinical staff medical and nursing must be cognisant of the content of this document

TABLE OF CONTENTS

1 Purpose/Scope

This document provides guidelines for the prescription and application of Laceraine® gel topical anaesthetic for the management of minor wounds in the Emergency Department (ED)

2 Responsibilities

Management is responsible for ensuring that registered nurses (RN) and medical officers who undertake this practice are provided with appropriate knowledge and training.

3 Product Information

Laceraine® is a sterile anaesthetic product for topical application to superficial wounds and lacerations to provide local anaesthesia.

Composition

Laceraine® is a mixture of:

Lidocaine (Lignocaine) hydrochloride 4.2% w/v (42.4 mg/mL)
Tetracaine (Amethocaine) hydrochloride 0.5% w/v (5 mg/mL)
Adrenaline (Epinephrine) 0.2% w/v (1.8 mg/mL) [1, 9]

Availability

Laceraine gel: 4mL glass vial, light protected (green cap) – NOT refrigerated

Laceraine gel topical wound anaesthetic contains no antimicrobial preservative. Use in one patient on one occasion only and discard any unused product. Do not use if gel is discoloured. If the plastic cap is lifted or removed the product should not be used.

Action

The local anaesthetic agents decrease sensory nerve impulse transmission. Adrenaline increases the duration of local anaesthetic action and decreases systemic absorption of the anaesthetics. In addition, adrenaline reduces the amount of blood in the wound field which may facilitate wound inspection and closure.

Efficacy

When applied to the wound as recommended, Laceraine® provides an effective level of local anaesthesia in the majority of patients. Duration of anaesthesia is 45 to 60 minutes following removal.

Absorption of Laceraine® from wound surfaces is low. In cases where topical anaesthesia alone is sub-optimal, lignocaine 1% -/+ adrenaline may be infiltrated prior to wound closure. The maximum additional lidocaine dose is 1 mg/kg = 0.1 mL/kg of 1% lignocaine with the total lidocaine dose not exceeding 5 mg/kg. Laceraine® must not be injected nor should it be applied following direct infiltration of Lidocaine +/- adrenaline.

4 Indications

Laceraine® is suitable for superficial lacerations and wounds that are likely to require closure with skin glue or sutures in the Emergency Department. It may also facilitate thorough cleaning, irrigation and debridement of painful minor wounds.

5 Contraindications and Precautions

Contraindications [1]

- Allergy or hypersensitivity to any components
- Use in children < 1 year of age is not recommended
- Wounds with end arteriolar supply due to vasoconstriction and risk of ischaemia: includes digits, ear pinnae, tip of the nose and penis
- Wounds greater than 5cm in length
- Wounds involving deep structures such as bone, cartilage, tendon, nerve or major vessels
- Contaminated wounds or human/animal bites, or deep punctures
- Wounds of mucous membranes, eyes, dental/oral injuries
- Not for use on intact skin or mucous membranes
- Burns
- Prior infiltration with local anaesthetic agent
- Trivial wounds unlikely to require repair
- Patients on monoamine oxidase inhibitors (MAOI's) within the last 14 days, digoxin, quinidine or propranolol

Precautions

- Wounds adjacent to mucous membranes or eyes: protective precautions should be used to avoid leakage or rubbing into the eyes or mouth.
- Flap lacerations where vasoconstriction is likely to cause tissue ischaemia.
- Patients with epilepsy, asthma, circulatory failure, hepatic or renal dysfunction, cardiovascular disorders, circulatory failure/hypovolaemia or shock, diabetes mellitus/peripheral vascular disease.
- If any adverse or systemic events are identified then the Laceraine® occlusive dressing should be immediately removed, the wound irrigated and urgent clinical review obtained.

6 Patient Assessment

Prior to the application of Laceraine® a focused patient and wound assessment should be undertaken by either the Clinical Initiatives Nurse, in conjunction with the triage assessment, or by the prescriber/treating clinician. The assessment should include:-

- Primary survey
- Time and mechanism of injury (NAI assessment) and first aid measures
- Location of the wound
- Wound description such as length, width, depth if known, shape, tissue flap
- Possible involvement of deep structures (motor function, sensation, neurovascular)
- Possible foreign bodies or contaminants
- Allergies
- Previous medical history and medications
- Immunisation status
- Pain score and analgesia used prior to arrival or initiated at triage
- Weight
- Fasting time: keep nil by mouth

7 Dose Calculations

Gel: **0.1mL/kg to a maximum of 2mL for children aged 1 to 3 years**

0.1 mL/kg to a maximum of 3mL for age 3 years to adult

Recommended doses should not be exceeded. The smallest effective dose should be applied and the volume documented in the Medication Administration Record (MAR) utilising the Electronic Medication Management (eMM) system.

Wounds should not require volumes greater than the dose limits for lacerations less than 5cm in length OR 1 mL for each cm of laceration, whichever is the lesser volume. Laceraine® should have direct wound contact for a minimum of 20 minutes and a maximum of 60 minutes.

The Laceraine® dressing and residual product is to be removed after 60 minutes to avoid excess absorption. Laceraine® application under a Standing Order by RN's is limited to a single prescription order. Additionally, no more than 4 doses in 24 hours should be prescribed or applied.[11]

8 Side Effects

The parent/carer (and patient where relevant) should agree to the proposed application and be informed of the expected response. Laceraine® may sting briefly on initial application.
The affected body part should be positioned and supported to ensure minimal movement during application.
Care should be taken to avoid product leakage or transfer from the site of application to the child's eyes, mouth or any other mucous membranes.
Laceraine® usually causes temporary blanching of local surrounding tissue indicative of effective absorption. This resolves over the ensuing hour as the medication wears off.

9 Administration

1. The dose must be prescribed by a Medical Officer, Nurse Practitioner or Accredited Registered Nurse as per SCHN Safe Prescribing Practice Guideline 2017 on the medication administration record (MAR).
2. The RN administering the Laceraine® draws up the prescribed dose of Laceraine® after removing the cap, metal collar and bung from the vial. Discard the unused portion. This product is for **topical use only**.
3. Gently clean the wound of surface blood, clot or debris. This facilitates effective wound contact of the Laceraine® with the wound surface and margins. Thorough cleaning and irrigation can be undertaken after the wound has been anaesthetised.
4. Apply Laceraine® gel directly to the wound ensuring full coverage. Use of a cotton tip applicator may facilitate spread/coverage. Avoid excess volume which may cause run-off or leakage.
5. Apply an occlusive clear film dressing (e.g. AsGuard ®, Tegaderm ®, Opsite ®). No cotton wool/gauze is required under the occlusive dressing. Application of barrier film (Cavilon®, Skin Prep®) to surrounding intact skin may aid dressing retention and removal.
6. Document the actual volume applied to the wound when signing the MAR.
7. Leave the occlusive dressing in place for a minimum of 20 minutes to a maximum of 60 minutes. Remove after 60 minutes.
8. Evaluate the therapeutic anaesthetic and analgesic and response.
9. Clean and/or irrigate the wound ensuring all Laceraine® is removed.
10. Complete the wound inspection and repair as appropriate.
11. Document the procedure.

10 Related Documents

- Safe Prescribing Guideline SCHN 2017
- Hand Hygiene
- Laceration Management in the Emergency Department
- NSW Health, Safety Notice, 2020: The Risk of Toxicity from Topical Anaesthetic Products https://www.health.nsw.gov.au/sabs/Documents/2020-si-003.pdf
- Standing Order SCH http://webapps.schn.health.nsw.gov.au/epolicy/policy/5408

11 References/resources

1. Phebra product information, Laceraine® Topical Wound Anaesthetic, Phebra Pty Ltd, 2020
2. NHMRC 2011, Emergency Care Acute Pain Management Manual, Page 37 http://www.nhmrc.gov.au/_files_nhmrc/publications/attachments/cp135_emergency_acute_pain_management_manual.pdf viewed 22 June 2018
3. Baren, J. M., Rothrock, S. G., Brennan, J. A. And Brown, L. Approach to Pain Management. Pediatric Emergency Medicine, 2008: Page 1111, Chapter 158. Saunders Elsevier, Philadelphia.
4. Hatfield, L. Messner E. and Lingg K. Evidence Based Strategies for the Pharmacological Management of Pediatric Pain During Minor Procedures in the Emergency Department. Topics In Emergency Medicine 2006; 28(2):129-137.
5. Hsu, D. C. 2018, Topical anesthetics in children, UpToDate, viewed 21 June 2018, <http://www.uptodate.com/contents/topical-anesthetics-in-children>
6. Tarsia, V et al. Percutaneous Regional Compared with Local Anaesthesia for Facial and Scalp Lacerations: a randomised control trial. Emergency Medicine Journal 2005; 22: 37-40.
7. The NSW Nurses' Association, Guidelines on Nursing Responsibilities in Relation to Medications, 2007, confirmed 2016, 5-6.
8. NSW Health Medication Handling in Public Health Facilities, viewed 3rd March 2020 http://www1.health.nsw.gov.au/pds/ActivePDSDocuments/PD2013_043.pdf
9. TGA, Updating medicine ingredient names. Viewed 21 June 2018. https://www.tga.gov.au/updating-medicine-ingredient-names-list-affected-ingredients#active
10. NSW Health, Safety Notice: The risk of toxicity from topical anaesthetic products, viewed 22 October 2020 http://internal.health.nsw.gov.au/quality/sabs/pdf/2020-si-003.pdf
11. Australian Medicines Handbook Children's Dosing Companion https://childrens.amh.net.au.acs.hcn.com.au/monographs/lidocaine-tetracaine-adrenaline#lidocaine-tetracaine-adrenaline-dosage

13.2. Attachment 2: Therapeutic Guidelines – 01/09/2021

Topical local anaesthetics for acute pain management

Local anaesthetics can be applied topically to the skin or a mucosal surface. The degree of skin penetration and effect depends on the dose, formulation and duration of skin contact. Topical administration is noninvasive and produces minimal adverse effects. It is useful for:

- wound debridement, including venous ulcer debridement (see Mechanical wound debridement and Conservative sharp wound debridement)
- dressing changes
- venous access in children, or an anxious or needle-phobic patient
- mucositis
- eye procedures
- endoscopic airway procedures.

Topical local anaesthetic formulations commonly contain lidocaine, prilocaine or tetracaine (amethocaine). The dose required depends on the surface area to be anaesthetised, but should never exceed the maximum recommended dose for age and weight. See Table 1.23 for commonly used topical local anaesthetic formulations.

Commonly used topical local anaesthetic formulations (Table 1.23)

Formulation	Brand name	Other comments
lidocaine 2% oral liquid or gel	Xylocaine Viscous, Mucosoothe	used for oropharyngeal anaesthesia rinse the oral liquid or gel in the mouth or gargle for 30 seconds then spit out, or swallow for anaesthesia of the pharynx avoid food or drink for 1 hour after application used for dressing changes
lidocaine 0.5%, 1% or 2% solution for injection	Xylocaine	remove as much of the wound dressing as possible, then soak the remaining dressing with lidocaine solution and leave for 10 minutes. Remove remaining dressing once area is anaesthetised do not exceed maximum recommended dose used in children before venepuncture or intravenous cannulation
lidocaine 4% liposomal cream	LMX4	1 g of lidocaine 4% liposomal cream contains lidocaine 40 mg. A 1 g dose is achieved by squeezing a length of 5 cm from the 5 g tube or 3.5 cm from the 30 g tube do not clean skin surface with alcohol or acetone before application because the cream has to mix with skin surface oils to be absorbed after application, cover the area with an occlusive dressing anaesthesia lasts 1 to 2 hours after removal of the cream

Formulation	Brand name	Other comments
lidocaine 2.5% + prilocaine 2.5% cream or patch	EMLA Numit	used for venepuncture, intravenous cannulation or minor dermal procedures (eg leg ulcer debridement) 1 g of cream or one patch contains lidocaine 25 mg and prilocaine 25 mg a 1 g dose of cream is achieved by squeezing a circular blob of cream the size of a small coin ($2), or by squeezing a length of approximately 3.5 cm from the tube after application, cover the area with an occlusive dressing anaesthesia lasts 2 hours after removal of the cream or patch
lidocaine 4% + tetracaine (amethocaine) 0.5% + adrenaline (epinephrine) 0.1% topical solution—also known as ALA	Laceraine	combination product available in some hospitals for topical application to superficial wounds and lacerations less than 7 cm ineffective on intact skin soak cotton wool balls in the solution then hold in place over the laceration with a dressing used for venepuncture or intravenous cannulation do not apply to broken skin
tetracaine (amethocaine) 4% gel	Local AnGel	1 g of AnGel contains tetracaine 40 mg. A 0.5 g dose of AnGel is achieved by squeezing a circular blob of gel the size of a small coin ($2) after application, cover the area with an occlusive dressing anaesthesia lasts 4 to 6 hours after removal of the gel
tetracaine (amethocaine) 0.5% or 1% eye drops	Minims Amethocaine	use for short ophthalmic procedures only (eg corneal foreign body removal) anaesthesia lasts up to 20 minutes never prescribe for home use if other eye drops are to be used during the procedure, instil tetracaine drops first because they reduce the initial stinging of subsequent eye drops, and increase their intraocular permeability

If **lidocaine 2% oral liquid or gel** is indicated for oropharyngeal anaesthesia, use:

lidocaine 2% oral liquid or gel, rinse in the mouth or gargle for 30 seconds then spit out, or swallow for anaesthesia of the pharynx, every 3 hours as needed. Avoid food or drink for 1 hour after application

child younger than 3 years: up to 0.2 mL/kg (maximum 1.25 mL). Do not exceed 4 doses in 24 hours. It may be necessary to apply the liquid or gel with a cotton swab

child 3 to 12 years: up to 0.2 mL/kg (maximum 5 mL). Do not exceed 4 doses in 24

hours

adult and child older than 12 years: up to 15 mL. Do not exceed 8 doses in 24 hours.

If **lidocaine 4% liposomal cream** is indicated (eg for venepuncture or intravenous cannulation), use:

lidocaine 4% liposomal cream, applied to skin that has not been cleaned with alcohol or acetone. Cover the area with an occlusive dressing after application. Anaesthesia lasts for 1 to 2 hours after the cream has been removed

infant 1 to 3 months: up to 1 g left on the skin's surface for no longer than 60 minutes

infant 3 to 12 months: up to 1 g left on the skin's surface for no longer than 4 hours

adult and child older than 1 year: up to 2.5 g left on the skin's surface for no longer than 5 hours.

If **lidocaine 2.5% and prilocaine 2.5%** cream is indicated (eg for venepuncture, intravenous cannulation, minor dermal procedures), use:

lidocaine+prilocaine 2.5%+2.5% cream applied to skin. Cover the area with an occlusive dressing after application. Anaesthesia lasts 2 hours after the cream has been removed

infant younger than 3 months: up to 1 g left on the skin's surface for 1 hour

infant 3 to 12 months: up to 2 g left on the skin's surface for 1 to 4 hours

child 1 to 6 years: up to 10 g left on the skin's surface for 1 to 4 hours

child 6 to 12 years: up to 20 g left on the skin's surface for 1 to 4 hours

adult and child older than 12 years: up to 60 g on intact skin, or 10 g on leg ulcers, left on the skin's surface for 1 to 4 hours (30 minutes may be sufficient for leg ulcers).

If **lidocaine 2.5% and prilocaine 2.5%** patches are indicated (eg for venepuncture, intravenous cannulation, minor dermal procedures), use:

lidocaine+prilocaine 2.5%+2.5% patches applied 1 hour before the procedure. Anaesthesia lasts 2 hours after the patch has been removed

infant younger than 3 months: 1 patch left on the skin's surface for no longer than 1 hour

infant 3 to 12 months: up to 2 patches left on the skin's surface for no longer than 4 hours

adult and child older than 12 months: up to 5 patches left on the skin's surface for no longer than 4 hours.

If **lidocaine 4% and tetracaine (amethocaine) 0.5% and adrenaline (epinephrine) 0.1%** topical solution is indicated (eg for superficial wounds and lacerations less than 7 cm), in adults and children 1 year or older, use:

lidocaine + tetracaine (amethocaine) + adrenaline (epinephrine) 4%+0.5%+0.1% topical solution: 0.1 mL/kg or 1 mL per cm of laceration (whichever is the smaller volume), up to 5 mL. Soak cotton wool balls in the solution, place on the laceration and hold in place with a dressing. Leave for 20 to 30 minutes (maximum 60 minutes). Do not exceed 4 doses in 24 hours.

If **tetracaine (amethocaine) 4%** gel is indicated (eg for venepuncture, intravenous cannulation), in adults and children older than 1 month, use:

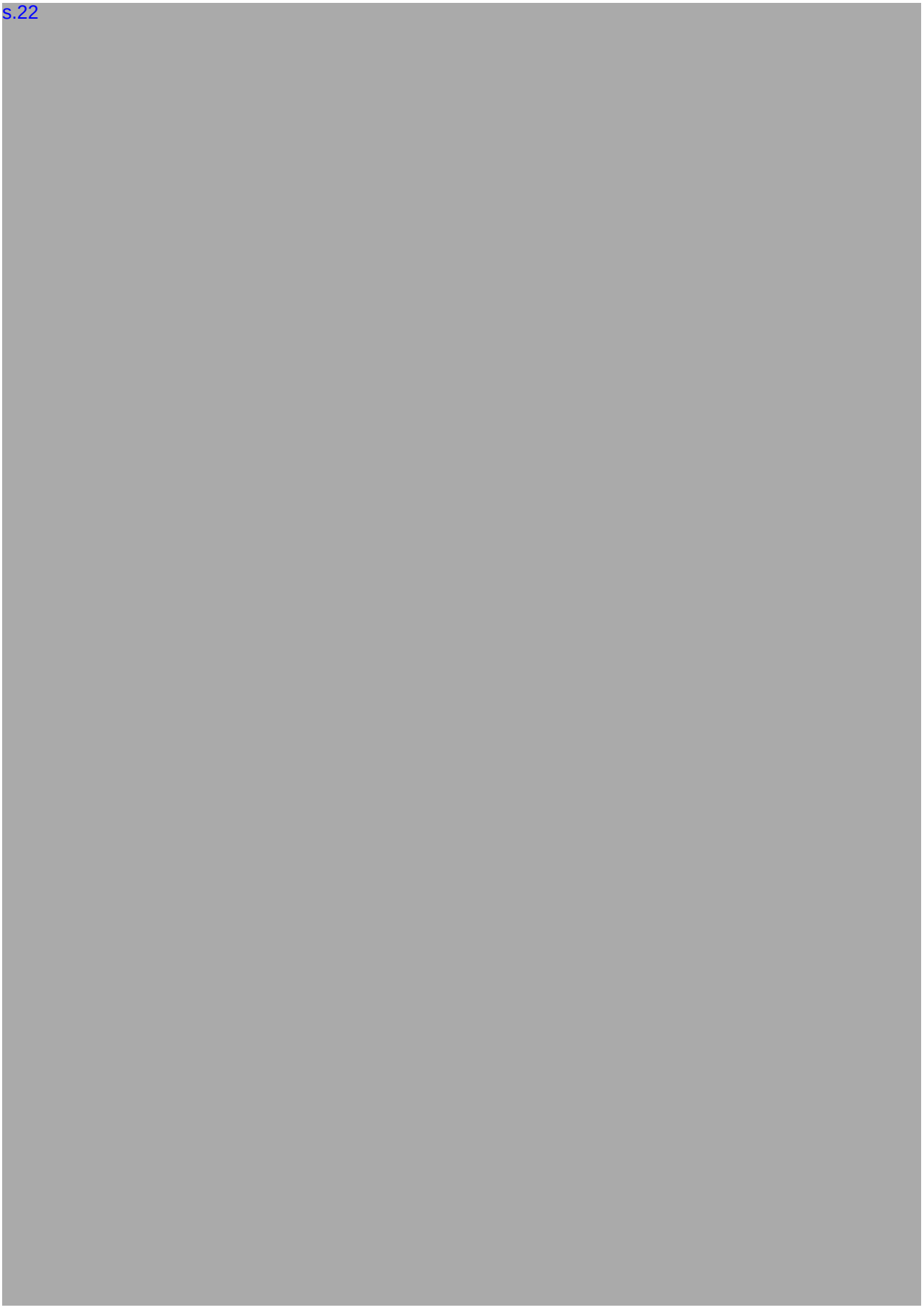
tetracaine (amethocaine) 4% gel 0.5 g, applied to intact skin for up to 1 hour. Cover

the area with an occlusive dressing after application. Anaesthesia lasts 4 to 6 hours after the cream has been removed.

If **tetracaine (amethocaine) 0.5% or 1%** eye drops are indicated for short ophthalmic procedures, in adults and children older than 1 month, use:

tetracaine (amethocaine) 0.5% or 1% eye drops: 1 drop into the affected eye; repeat after 5 minutes if required.

s.22



Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
https://www.tga.gov.au

Attachment 4

OM-2022-00069-1 - Phebra Pty Ltd - Laceraine® Gel Topical Wound Anaesthetic - N5

New OTC medicine - Evaluation of Quality

FN: E22-631855/ E22-527454
Sequence: e006280 (0000)
Edata: D22-5178216

Background

Phebra Pty Ltd seeks to register a sterile gel containing a new fixed dose combination of 4.266% lidocaine (lignocaine) hydrochloride monohydrate (equivalent to 4% lignocaine HCl), 0.5% tetracaine (amethocaine) hydrochloride and 0.18% adrenaline (epinephrine) acid tartrate. The trade name proposed for the product is 'Laceraine® Gel Topical Wound Anaesthetic' and the suitability of this moniker will be assessed separately.
The cover letter (dated 30 September 2021) is included below.

cover.pdf

No other products are registered in Australia that contain this combination of drug substances. There are also no (Australian) registered products containing combinations of adrenaline acid tartrate and tetracaine HCl or lidocaine HCl and tetracaine HCl, however the combination of adrenaline acid tartrate and lidocaine HCl is used in a number of solution for injection products. Furthermore, solution and gel formulations of the proposed drug substance combination have been used as unapproved medicines in the UK since 1995 and as a registered product in NZ since 2006. s.47

The proposed ARTG indication for the product is for topical application to superficial wounds and lacerations to provide local surface anaesthesia for wound closure. It may be used to provide topical anaesthetic relief for cleaning, irrigation and debridement of painful minor wounds. The product should only be used topically on broken skin.
The product will be presented as s.47 The product is a clear, colourless to straw-coloured, semi-liquid application.

This evaluation only concerns the chemistry and quality aspects of the submission. Clinical (D23-5165197), microbiological (D22-5679265) and presentation (labelling, PI and CMI) aspects have been evaluated separately.

Relevant BP and USP monographs are included below.

s.47

s.47

Attachment 4

s.47

s.47

Quality

Module 3.2.S: Drug Substance

Quality control of the drug substances

Lidocaine HCl monohydrate

Lidocaine HCl monohydrate is supplied by s.47 Its manufacture and quality control, s.47 , have been assessed by s.47 s.47

The specification and analytical methods applied to lidocaine HCl monohydrate by the finished product manufacturer are s.47

Tetracaine HCl

Tetracaine HCl is supplied s.47 Its manufacture and quality control, s.47 have been assessed by s.47

The specification and analytical methods applied to tetracaine HCl by the finished product manufacturer are s.47

Adrenaline Tartrate

Adrenaline tartrate is supplied s.47 Its manufacture and quality control have been assessed, s.47

The specification and analytical methods applied to adrenaline tartrate by the finished product manufacturer s.47

Attachment 4

Module 3.2.P: Drug product

3.2.P.1: Description and composition of the drug product

The product is described as a clear, colourless to straw coloured, particle-free, non-greasy, uniform semi-liquid application of moderate viscosity with free-flowing properties. Formulation details are reproduced below.

Active Ingredient	Quantity (mg/mL)	Overage (%)	Function	Reference to Standard
Lidocaine (lignocaine) hydrochloride monohydrate	42.66*	s.47	Active	s.47
Tetracaine (Amethocaine) hydrochloride	5.0		Active	
Adrenaline acid tartrate	1.8		Active	

*Equivalent to 40 mg/mL lidocaine hydrochloride.

Excipient Ingredients	Quantity (mg/mL)	Overage (%)	Function	Reference to Standard
Sodium metabisulfite	s.47			
s.47				
Water for injections in Bulk (WFI)	s.47			
s.47				

3.2.P.2: Pharmaceutical Development

3.2.P.2.1: Components of the Drug Product

The drug substances (lidocaine HCl monohydrate, tetracaine HCl and adrenaline tartrate) are all water soluble. s.47

3.2.P.2.2 Drug Product Development

s.47

Apart from the WFI, s.47

For these reasons, s.47 [redacted]

s.47 [redacted]

3.2.P.2.3 Manufacturing Process Development

The manufacturing process involves s.47 [redacted]

Considerations in the design of the manufacturing process were adequately described. In particular, s.47 [redacted]

3.2.P.2.4 Container Closure System

See under 3.2.P.7, below.

3.2.P.3. Manufacture

The product will be manufactured s.47 [redacted]

s.47 [redacted]

The manufacturing process flow chart is reproduced below. s.47 [redacted]

Attachment 4

Manufacturing process validation data s.47

[redacted]

s.47

[redacted]

Attachment 4

s.47 [redacted]

3.2.P.4. Control of Excipients

Sodium metabisulfite, s.47 and water for injections are stated to comply with the s.47 Certificates of analysis were provided from the excipient suppliers for sodium metabisulfite and s.47 s.47 [redacted]

s.47 [redacted]

Excipients of Animal Origin

s.47 [redacted]

3.2.P.5. Control of Drug Product

3.2.P.5.1 Specifications

The proposed drug product specification is included below.

PDF

s.47 [redacted]

The following points are noted:

- For each drug substance s.47 [redacted]
- Lidocaine HCl assay s.47 [redacted]

Attachment 4

s.47

- Tetracaine HCl assay s.47
- Adrenaline tartrate assay is s.47
- Related substances limits (release and expiry) are included for: s.47
- **The s.4 limit at release is s.47 and at expiry is s.47**
- **The s.47 limit is s.47 at release and s.47 at expiry.** s.47
- The s.47 and the limits are stated to comply with s.47

- Sterility limit is s.47 Sterility aspects of the submission have been assessed separately.
- s.47
- s.47

3.2.P.5.2 Analytical Procedures

Th s.4 method (based on s.47) was adequately described.

No method descriptions for s.47 The specification document indicates that s.47 methods are used to measure s.47 and the microbiological assessment (D22-5679265) has requested confirmation of this. The specification references s.47 for the s.47 so it will be assumed that the s.47 are used. s.47

Lidocaine assay s.47
Lidocaine HCl and s.47 are measured using a s.47 under the following conditions:

s.47

Attachment 4

s.47 [redacted]

Tetracaine HCl assay and s.47 determination

Tetracaine HCl and s.47 are measured using s.47 under the following conditions:

s.47 [redacted]

Tetracaine HCl and s.47 are measured s.47 [redacted]

s.47 [redacted]

Attachment 4

s.47 [redacted]

s.47 [redacted] determination
s.47 [redacted] is determined s.47 [redacted] under the following conditions:

s.47 [redacted]

s.47 [redacted]

Determination of Adrenaline Tartrate

Adrenaline tartrate assay is measured s.47 [redacted] under the following conditions:

s.47 [redacted]

s.47 [redacted]

[redacted]

Attachment 4

s.47

For all of the s.47 presented the calculations are s.47

3.2.P.5.3 Validation of Analytical Procedures

Lidocaine HCl assay

Validation results were s.47

s.47

Validation results were presented with regard t s.47

Tetracaine HCl assay

Validation results were presented with respect to s.47

s.47 determination

The validation data presented for s.47 included information showing that the method can also s.47 . It is noted in the validation report that the s.47 As noted above, the method used in the validation study appears to s.47

For s.47 was demonstrated s.47 and for s.47 was demonstrated s.47 s.47 were demonstrated for s.47

s.47

The method was validated with respect to s.47

Adrenaline tartrate

The method was validated with respect s.47

Attachment 4

s.47 [redacted]

3.2.P.5.4 Batch analyses

Analytical data were provided for production scale batches s.47 [redacted] The results showed s.47 [redacted]. The assays for lidocaine HCl, tetracaine HCl and adrenaline tartrate were s.47 [redacted] The specified impurities s.47 [redacted]

3.2.P.5.5 Impurities

The quality of each drug substance is controlled by s.47 [redacted]. Of the impurities s.47 [redacted]

Of the impurities s.47 [redacted]

Of the impurities s.47 [redacted]

In line with s.47 [redacted]

3.2.P.5.6 Justification of specifications

See comments in section 3.2.P.5.1.

3.2.P.6 Reference standards or materials

Certificates of analysis were provided for the following reference standards:

- Lidocaine s.47 [redacted]

- Tetracaine HCl s.47
- Adrenaline tartrate s.47

3.2.P.7 Container

The viscous product liquid is filled into s.47 A certificate of analysis from the supplier was provided. The vials are sealed s.47 . The stoppers are s.47 A certificate of analysis from the supplier was provided. The stoppers are sealed s.47 A certificate of analysis from the supplier was provided.

The company will be asked to provide certificates of analysis from the finished product manufacturer's testing of the container closure components.

3.2.P.8 Stability

3.2.P.8.1 Stability summary and conclusion

The proposed shelf life for the unopened product is s. months (when stored below 25°C).

3.2.P.8.2 Post-approval stability protocol and stability commitment

Commitment was provided that s.47

3.2.P.8.3 Stability data

The following production scale batches have been placed s.47

The batches were manufactured according to the proposed manufacturing process/ batch formula and the solution/ gel was stored in the proposed vials/ container closure system. The vials were stored s.47 The following parameters will be tested after s.47 months in the s.47 trials and after s.47 in the s.47 trials: s.47 It is assumed that the methods described in Section 3.2.P.5.2 were used in the analysis.

Attachment 4

Results

The following points are noted:

- s.47 [redacted]

s.47 [redacted]

Conclusion

The proposed shelf life and storage conditions might be OK. s.47 [redacted]

Summary of Issues

The following issues should be addressed:

Drug product

1. The manufacturing process flow chart indicates that s.47 [redacted]

Attachment 4

2. Please consider including s.47

3. The manufacturing process validation studies included s.47 conducted on the bulk mixture were provided that s.47

4. No testing s.47 Please provide certificates of analysis for s.47 as tested by the finished product manufacturer together with an assurance s.47

5. Please address the following points with regard to the proposed s.47

   a. For each drug substance a s.47

   b. Long term stability results show s.47

   c. The tetracaine assay shows s.47 .

   d. s.47 the adrenaline tartrate assay s.47

   e. The limit for s.47 appears to be s.47 While the approach of matching impurity limits with those in relevant compendial monographs (rather than ICH limits) is accepted, s.47

   f. The limit for s.47 is s.47 .

   g. Appropriate limits should be included for s.47

   h. The s.4 limit at release is s.47 and at expiry is s.47 . No decreases were observed for s.4 in the stability trials and results were in the range s.47 The release and expiry limits should be adjusted accordingly.

Attachment 4

i. The s.47 limit is s.47 at release and s.47 at expiry. s.47 in s.47 were observed in s.47

j. Please include appropriate release and expiry limits for s.47 urthermore, aged batch data should be included to demonstrate that the proposed limit at expiry is met.

6. The following points, with regard to the analytical methods, should be addressed.
   a. Please provide a brief outline of how s.47 is measured.
   b. Explanation should be provided for the differences s.47 urthermore, the method s.47
   c. Evidence should be provided that either s.47 can measure s.47
   d. For all of s.47 presented the s.47 Please explain how the s.47

7. In line with the s.47 , a s.47 risk assessment should be conducted at the product level in line s.47 If necessary, s.47

8. Please provide certificates of analysis from the finished product manufacturer's testing of the container closure components.

9. The s.47 observed in the s.47 with respect to s.47 and the sole s.47 should be addressed (as noted above). Consideration should be given to s.47

10. Comment is also sought on the possibility that the s.47 drug substance might s.47 and what effect this might have on the quality of the product.

s.22
22/3/2023

Attachment 4

S31 Response

The company has responded (D23-2730517) to the TGA's s31 request (D23-5326043). The response and cover letter are included below.

PDF s.47 [redacted]

PDF s.47 [redacted]

Evaluation of Module 3 responses

1. An updated manufacturing process flow chart was provided that now matches the manufacturing process description and includes the overnight cooling step.

2. The company has declined to s.47 [redacted]

3. Assurance was provided that comprehensive s.47 [redacted] will be conducted s.47 [redacted]

4. As requested, certificates of analysis were provided for the s.47 [redacted] (as tested by the finished product manufacturer). Assurance was provided that s.47 [redacted]

5. An updated drug product specification was provided (below)

   PDF s.47 [redacted]

   The following points are noted:

   a. As requested, a s.47 [redacted]

   b. The company was asked to s.47 [redacted] The original request was made on the basis of the evaluator's faulty s.47 [redacted]

   c. As requested, the s.47 [redacted]

   d. As requested, the s.47 [redacted]

   e. As requested, a limit s.47 [redacted] has been added to the specification. The limit is in s.47 [redacted]

f. s.47 have been included for: s.47

The limits for s.47 The limits for s.47 are commensurate with the limit for s.47

While it is probably OK to have s.47

g. Limits have now been included s.47 and s.47 but only for s.47 . It is noted that the s.47 s.47 does not include s.47 limit but the s.47 while the s.47 doesn't include s.47 at all. Given the varied approaches taken s.47

h. The s.4 limits have been s.47 from s.47 at release and s.47 at expiry to s.47 at release and s.47 at expiry. The stability data showed values in the range s.47 . The updated limits are accepted.

i. The s.47 limits have been tightened from s.47 at release and s.47 at expiry to s.47 at release and s.47 at expiry. The proposed limits are aligned with the stability results and they are accepted.

j. No s.47 limit has been included for the s.47

6. The following points, with regard to the analytical methods, are noted.
   a. As requested, s.47
   b. Clarification was provided regarding s.47

s.47 The method has been modified to include the measurement s.47

c. A new s.47 to measure s.47 has been developed, which was allegedly based on the one described in s.47

d. Adequate explanation was provided for all of the calculations.

7. A risk assessment for s.47 has been conducted in line with s.4 . The results show tha s.47

8. As requested, specifications and representative certificates of analysis from the finished product manufacturer were provided for s.47

9. The s.47 observed in the stability studies with respect to s.47 has been addressed with s.47 Updated stability data were provided for the original stability batches, s.47 However, stability data were also provided for s.47 that have been stored for up to s. months (storage conditions not specified), which appeared to show that s.47

for the s.47 Levels of the s.47 were recorded at low levels. The company propose a s.47 (store below s.47 to allow more s.47

10. An argument was presented to support the company's contention that s.47 Firstly, the drug product manufacturer s.47 at the drug substance stage s.47 Then, so the argument goes, s.47 is s.47 dependant and the s.47 and above. The expiry drug product specification allows a s.47 for the product of s.47, so in principle s.47

Recommendation

Approval of the product from a chemistry and quality perspective is not yet recommended. As noted above, a further update to the s.47 (noting this may be difficult with such limited data available). Furthermore, the company is s.47 and include an s.47

s.22
8/9/2023

2nd s31 Response

The company has responded (D23-3910138) to the TGA's second s31 request (D23-3480585). The response and cover letter are included below.

PDF s.47 PDF s.47

Evaluation of Module 3 responses

1. An updated s.47 was provided (included below).

PDF s.47

The following points are noted:

- A release limit of s.47 has been included for s.47 The limit was s.47 aged batch results and the newly provided release results for s.47 It is accepted that the new s.47 represents a s.47 in conjunction with the expiry limit of s.47 and a shelf life of s.47 months.

- The release limits for s.47 have been

tightened. The release limits for s.47 [redacted] hese limits are accepted.

- The limit for s.47 [redacted] which was previously aligned with the limit of s.47 [redacted] (release and expiry) in the s.47 [redacted], has now been changed to s.47 [redacted] at release and s.47 [redacted] at expiry. Stability data show levels of the impurity reach about s.47 [redacted] after s. [redacted] months storage. The proposed limit is s.47 [redacted] The company has justified s.47 [redacted] with references that suggest the s.47 [redacted]

- Release s.47 [redacted] and expiry s.47 [redacted] have been proposed for s.47 [redacted] s.47 [redacted]. The aged batch data show that levels of [redacted] upon storage. After s.47 [redacted] The proposed limits appear s.47 [redacted]

2. A method for measuring s.47 [redacted] in the product was described in which the s.47 [redacted] **. The method was validated** s.47 [redacted]

Recommendations

Toxicological advice has been received s.47 [redacted]

The company will be asked to s.47 [redacted] and then reconsider s.47 [redacted] The proposed method s.47 [redacted] so the

Attachment 4

s.47 experiments, which were conducted using the product gel, s.47

s.22
10/11/2023

3rd s31 Response

The company has responded (D24-684388) to the TGA's 3rd s31 request (D24-277004). The response and cover letter are included below.

PDF s.47 PDF s.47

Evaluation

1. The company has committed to s.47

   PDF s.47

   s.47 with the updated specification, the company propose a shelf life for the product of s.47 . No s.47

   The proposed shelf life is accepted, given that s.47

2. The proposed method for s.47 , in which the gel is dispersed s.47

   Whilst the s.47

Recommendation

Approval of the product, from a chemistry and quality perspective, is recommended.

s.22
28/2/2024

2.5 CLINICAL OVERVIEW

Table of Contents

2.5.1 Product Development Rationale

When patients present to an emergency department (ED) with superficial wounds or lacerations, current medical practice is to use a topical anaesthetic product to facilitate the cleaning and repair of the wound. This practice is confirmed internationally by hospital guidelines, published medical literature, and supported by the Cochrane review (Tayeb 2017).

s.47 The product contained a combination of lidocaine, adrenaline and tetracaine [also referred to as ALA, standing for **A**methocaine/**L**ignocaine/**A**drenaline, Lawton 2014].

In response, Phebra developed a sterile solution containing the LAT combination based on a sterile product produced by Torbay Pharmacy, connected to the South Devon Health Care NHS Trust, in the United Kingdom (UK). The Torbay product (since reformulated to a gel, known as 'LAT Sterile Gel') has been compounded and supplied to UK hospital pharmacies since 1995 and remains available on Torbay's current product listing (as unlicensed, not approved through a regulatory process). A similar LAT solution, Topicaine®, has been available as a commercial registered product in New Zealand since 2006. Phebra has manufactured and supplied a sterile solution containing the same active ingredients in the same concentrations (as LAT Sterile Gel and Topicaine) since 2004. s.47

Phebra's initial product, known as ALA, then subsequently Laceraine® Topical Wound Solution ('Laceraine solution') became widely used throughout Australia. While no adverse drug reactions had been reported in relation to the use of the product, s.47 a gel being preferred to a solution. The solution required the use of cotton balls or swabs for application and retention over the wound for a period of up to 60 minutes. Depending on the location of the wound, and the age or compliance of the child, it was often difficult to retain the soaked dressing in place or to contain runoff. The refrigerated solution was cold on application and, as with local anaesthetic agents in general, stung transiently which added to the challenges of placement and retention in young children. Additionally, there had been a case reported to Phebra by the s.47

s.47 [redacted]

Accordingly, Phebra developed Laceraine® Gel Topical Wound Anaesthetic ('Laceraine gel') with the equivalent active ingredients and concentrations as the solution, in a viscous methylcellulose base. The gel formulation has been manufactured since August 2020 and has now replaced the solution product. Phebra now propose to register the Laceraine gel.

2.5.1.1 Scientific Background and Rationale

Based on the available published data, the s.47 [redacted] it is considered that there is sufficient evaluable data of reasonable quality to support a literature-based submission (LBS) for Laceraine Gel Topical Wound Anaesthetic.

To support this LBS a justification for the fixed dose combination is provided in module 1.5.6.

2.5.1.2 Clinical Development, Regulatory History and Approval Status

2.5.1.2.1 Australian Medical Practice

Lacerations are a common reason for paediatric presentations to Australian emergency departments (ED) and other primary care facilities, such as general practice (GP) surgeries. Management of paediatric lacerations focuses on minimising pain and distress to allow thorough cleaning, debridement and surgical repair when indicated to optimise clinical outcomes (Lawton 2014).

The approach to managing acute pain in the paediatric population and anxiety should be multifaceted with attention to pharmacological and non-pharmacological measures. Initial pharmacological management in most Australian EDs comprises simple oral analgesia and topical application and/or local infiltration of local anaesthetic agents. This may be augmented with nitrous oxide inhalation to ameliorate anxiety and procedural discomfort.

The least noxious and optimally tolerated method of local anaesthetic application for minor wounds is via the topical route as occurs with Laceraine, a combination of 0.5% tetracaine, 4% lidocaine and 0.1% adrenaline. This preparation has been widely used in Australia for topical application since 2004.

2.5.1.2.2 Regulatory History and Approval Status

As each of the 3 active ingredients has been approved for decades and has well established use, no formal clinical development of the combination product has occurred.

A commercial LAT solution product was granted consent in New Zealand, following Medsafe approval on 21 December 2006 (Topicaine, TT50-7343). However, no other commercial product has been identified by Phebra, or through the searching methodology, as registered by a health authority with comparable regulatory standards to the TGA. However, similar products are manufactured in hospital pharmacy facilities internationally, as noted in the published clinical trials (CT).

s.47

2.5.1.3 The Design, Conduct, and Analysis of Studies Presented

The published clinical trials presented as the clinical data set were identified through a systematic literature search (in line with the Therapeutic Goods Administration's LBS requirements). As noted in module 2.7.3, 12 published studies were identified as relevant to provide efficacy data in support of Laceraine gel. Nine of these 12 studies are randomised controlled trials (RCT), conducted as phase 3/4 studies in ED, in essentially real-world settings.

2.5.2 Overview of Biopharmaceutics

Not applicable, as the active ingredients are well established, and the pharmacokinetics are well characterised for topical application (refer also module 1.5.6).

2.5.3 Overview of Clinical Pharmacology

Not applicable, as the active ingredients are well established, and their pharmacology well characterised for topical application (refer also module 1.5.6).

2.5.4 Overview of Efficacy

2.5.4.1 Efficacy in Indication

The combination of active ingredients and the doses of these ingredients have been well established over decades. While published trials reported minor differences in the doses of adrenaline (which varied from 1 in 2000 to 1 in 1000) and tetracaine (0.5 to 1.0%) these small differences reflect local medical practice in some cases. However, such minor differences in dose or concentration would be unlikely to affect efficacy or response, given the variability in contact time and individual patient and clinical need.

The efficacy of LAT combination products for the proposed indication – topical anaesthesia for laceration cleaning, assessment and/or repair – has been demonstrated.

The 12 published studies demonstrate:

- The efficacy of the combination and dose of the LAT solution
- Therapeutic equivalence of the LAT combination to an established comparator (TAC)
- Therapeutic superiority of the LAT combination to a placebo
- The therapeutic equivalence of the LAT solution and gel
- The improvements in utility of the LAT gel (over the solution)

Three studies (Schilling 1995, Ernst 1995 and Ernst 1995b) compared LAT with TAC. Adequate anaesthesia was equivalent for LAT solution and TAC solution in Schilling, with 74.4% and 79.5% of subjects showing no evidence of discomfort in the LAT and TAC groups respectively (χ^2 P=0.46). The study Ernst 1995 reported some differences between LAT solution and TAC solution with fewer painful sutures in the LAT group than the TAC group (P=0.036), and the physician ranked sum rating for pain scores was 41.6 for LAT and 54.6 for TAC (P=0.093). While this conclusion is somewhat challenging, the variabilities of each wound and the type, depth and number of sutures are not included, a similar number of patients in each group requested additional anaesthetic, confirming the experience that the final sutures placed may be less well anaesthetised, which is more likely to be related to technique than the product. In Ernst 1995b when LAT gel was compared with TAC gel there was no statistically significant difference between the number of sutures causing pain, 18% vs 13% (P=0.51). These studies concluded that LAT worked as well as TAC for topical anaesthesia.

The studies Alder 1998 and Harman 2013 compared LAT with an inactive placebo (sterile water in Alder 1998 and a placebo gel in Harman 2013)). The pain value was statistically significantly lower for LAT solution (4.0) than placebo (5.0; P<0.05) in Alder 1998, with only 13 subjects (43.3%) of the LAT group requesting additional anaesthesia, compared with 30 subjects (100%) in the placebo group. Harman 2013 reported that children receiving LAT gel reported less pain of application than those receiving the placebo gel: median (IQR) for LAT 0.50 (0.25-1.50) and placebo 1.00 (0.38-2.50) on the visual analogue score (VAS) and LAT 0.00 (0.00-2.00) and placebo 2.00 (0.00-4.00) on the Faces Pain Scale-Revised (FPS-R).

The study Resch 1998 made a direct comparison between LAT solution and LAT gel and showed equivalent levels of adequate anaesthesia: no evidence of discomfort in

75 subjects (82%) of the LAT gel group compared with 87 (84%) of the subjects in the LAT solution group (no significant difference).

Priestley 2003 reported no significant difference in the sedation rate (an indicator of inadequate anaesthesia). Ten subjects (12%) in the group receiving LAT at triage and 13 subjects (17%) in the control group (receiving adrenaline at triage) required sedation (P=0.46; χ^2).

In the uncontrolled studies Vandamme 2015 and White 2004 (both studies including use on digital lacerations) the proportion of subjects requiring additional anaesthesia was 23.6% and 46.3% respectively.

Most studies provided commentary on the improved utility of a LAT gel over a LAT solution. However, only 2 studies included a question about preference: Ernst 1997 noted in their conclusions that both patients (adults) and physicians preferred LAT gel as it was significantly less painful to apply (than the buffered lidocaine-adrenaline (LA) injection), while White 2004 reported the mean discomfort (VAS, for patients who were children) of the procedure in LAT successes was 2.7 while for LAT failures it was 6.7.

O'Connor 2010, Ernst 1997 and Lee 2013 noted the benefits of LAT compared with only injectable local anaesthetic. O'Connor noted that the introduction of LAT gel as a topical anaesthetic, significantly reduced the number of children with wounds referred to speciality teams for general anaesthesia. A total of 31 patients (15.4%) before the introduction of LAT gel and 15 (7.7%) after the introduction of LAT gel required general anaesthetic (P=0.018). Ernst 1997 reported significant difference in both physician and patient ratings of the pain of application of LAT solution (0 and 0 respectively) and injection of lidocaine with adrenaline (1.4 and 1.2 respectively); both comparisons P=0.001). Lee 2013 compared LAT gel with lidocaine infiltration (injection) in terms of the pain of application or injection. Patients reported a mean pain score of 1.5 for LAT gel and 3.5 for lidocaine (P<0.01).

This body of data reflects the Australian clinical experience of staff specialist appointments in ED's at s.47 [redacted] It has been frequently noted that correct application technique and adequate retention over the recommended time is necessary to assure efficacy - as evidenced by the resultant tissue blanching. It is particularly important in a mixed ED setting and other primary care facilities which are not specialised paediatric units, that correct application is simple and easy to achieve. This was an issue using the combination of Laceraine solution and cotton/gauze as a conduit when poor application resulted in sub-optimal contact with wound margins and therefore an inadequate anaesthetic effect. This has been remedied with the gel combination.

The gel does appear less painful, there is less run off and most importantly, leaves less room for interpretation or modification of application techniques. The case at s.47 [redacted] The incorrect application of Laceraine solution was quite common and often resulted in inadequate anaesthetic effect, the consequences of which required either re-application, infiltration of LA and occasional procedural sedation.

2.5.4.2 Demographics and Primary Disease Characteristics - Patient Population

The patient populations described in the 12 published CTs are considered representative of the patient populations who would receive Laceraine gel in Australia. While Laceraine products have more commonly been used in children, use in adults has increased in response to needle-phobia and anxiety, for whom a topical agent is beneficial in wound assessment and cleaning.

Similarly, the ED settings and protocols in the CTs regarding triage of patients and early commencement of clinical interventions, particularly for paediatric patients, are similar to protocols and guidelines in place in Australia (Therapeutic Guidelines 2021).

2.5.4.3 Relationships between Efficacy, Dose, and Dosage Regimen

The method of use and setting for use of the product focuses on acute superficial wound, single dose application. While there is some leeway to 'titrate' the dose by using slightly increased volume (up to the maximum dose) if the treating clinician judges that the wound/laceration warrants it, or by slightly extending the duration of the gel application to increase contact time (again if this is felt to be warranted), the dose is otherwise fixed. This is supported by the published CTs and reflects the experience of the EDs who have used LAT preparations as their topical anaesthetic of choice for decades.

2.5.4.4 Long Term Efficacy, Dosage, and Development of Tolerance

The indication for use of Laceraine in acute minor wound management is to facilitate effective cleaning assessment and repair of lacerations, in an ED or equivalent health care community setting. Therefore a single application is usually sufficient for the duration of the procedural activity. While there may be some situations in which re-application may be required to facilitate subsequent definitive care, there is generally no need for repeated administration. There may also be instances of multiple wounds when Laceraine gel may be used prior to local anaesthetic infiltration in children.

Overall, considerations of efficacy in the long-term, or concern in relation to the development of tolerance are not applicable to the proposed use of Laceraine gel.

2.5.4.5 Plasma Concentration Monitoring during Treatment

Not applicable, the product is applied topically for local effect. As systemic absorption is negligible (based on the vasoconstrictive action of adrenaline) there is no necessity to monitor plasma concentrations of the active ingredients.

2.5.5 Overview of Safety

2.5.5.1 Adverse Events Characteristic of Pharmacologic Class

Correctly applied topical local anaesthesia is highly unlikely to lead to adverse events.

The type of adverse events for the local anaesthetic ingredients (lidocaine and tetracaine) can be related to levels of systemic absorption (which in this setting is negligible), and to the possible adverse events due to the form and the dose. Theoretical adverse reactions to the gel if inadvertently spread into eyes or mouth, would include stinging and probably unpleasant taste. Management of leakage into eyes or mouth (based on local protocols) would include irrigation to ameliorate any side effects.

Tetracaine 0.5% eye drops are commonly used in children to remove eye foreign bodies or assess corneal abrasions therefore effects would be low risk and transient. Xylocaine Viscous gel is used as oral anaesthetic gel and is also transient and safe in the small quantities that may be involved. Adrenaline is used as a nebulised product (1:1000 solution at 0.5 mL/kg to a maximum of 5 mL) in small children with croup to reduce laryngeal oedema and obstruction. Despite frequently causing transient tachycardia, it is often safely repeated multiple times in cases of severe croup. With topical adrenaline there will unlikely be sufficient absorption or dosage to cause systemic effects such as transient tachycardia commonly associated with intravenous and nebulised adrenaline.

The type of adverse events for topically applied adrenaline as a single application would also be theoretical as the adrenaline component causes local constriction of capillary bed, reduced bleeding at the wound site. This is a desired effect in wound management as the blanching of affected tissues signifies that anaesthesia will likely have occurred and allows for identification of the zone of effective uptake prior to cleaning and closure. Reduced bleeding in the field facilitates improved examination of the wound base or deep structures, enhances the ability to identify and remove debris or foreign material and supports ease of suture placement if required. Adrenaline also prolongs the duration of the local anaesthetic agents. However, there may be a theoretical potential for vascular compromise to the viability of a skin or tissue flap that may contribute to devascularisation and impaired healing of that tissue. It is the clinical Australian experience that tissue flap ischaemia and resultant necrosis more often occur due to improper debridement and suturing technique, which are likely to bear a greater influence affecting outcomes in these types of wounds.

2.5.5.2 Extent of Exposure

The published clinical trials report no adverse events for the 955 subjects receiving LAT combination treatment.

The Australian clinical experience is that when applied according to directions, the combination product (Laceraine) is very safe and unlikely to cause adverse events.

To date there have been no reports of adverse drug reactions to Laceraine received by Phebra. s.47 this absence of reported adverse reactions indicates a very safe product.

2.5.5.3 Deaths and Serious Adverse Events

No deaths or serious adverse events have been reported.

2.5.5.4 Similarities and Differences in Results Among Studies

The safety profile of LAT combinations across the published CTs was consistent. There were no adverse effects (nor adverse reactions) reported. The only safety findings related to wound complications or infections, generally identified or reported during follow-up.

This is further supported by the Australian experience using both Laceraine solution and Laceraine gel.

2.5.5.5 Relation of AEs to Dose, Dose Regimen, and Treatment Duration

Not applicable, as no adverse drug reactions were reported, either in published CTs or directly to Phebra.

2.5.5.6 Long-term Safety

The recommended indication is for a single application in an acute clinical setting and as such the long-term safety is not applicable. The duration of treatment in published studies included contact of the product with the wound for a recommended maximum of 30 min (1 study included contact for 45 min). Anecdotal ED experience has found the safety and effectiveness of a window of application from 20 – 60 min is sufficiently flexible to offer effective anaesthesia, to manage most presentations in an appropriate timeframe.

There are circumstances where an uncooperative child may prematurely remove the dressing and re-application is required with reinforced retention. There may also be circumstances where surge activity in the ED precludes initial management as planned. The dressing is removed at 60 minutes and may need reapplication after an hour or more

to facilitate subsequent definitive care. Multiple wounds may have Laceraine applied but within the total dose limits. If upon testing sensation, a wound is deemed inadequately anaesthetised by Laceraine alone, ED guidelines provide the dose for additional infiltrated lidocaine which may be administered.

Therefore, individual patients are unlikely to receive repeated doses of the product in a frequency which would constitute 'long-term' use and therefore raise concerns for long-term safety.

2.5.5.7 Methods to Prevent, Mitigate, or Manage AEs

Given the safety and absence of adverse events reported, the usage of LAT combinations in ED, based on hospital protocols and guidelines clearly supports the safe use, and mitigates possible adverse events.

The gel formulation mitigates the earlier risks associated with the placement of soaked cotton wool or other conduit being retained in the wound, is generally less likely to be applied incorrectly and therefore improves efficacy of local anaesthesia.

Dosing limits and order sentences in electronic Medication Management software supports safe dosing limits for patients by age and weight.

ED clinicians can be guided by the proposed product information (PI) which provides clear instructions on dose, precautions and application technique. Local guidelines, protocols and education can reinforce safety and effectiveness.

Protocols recommend that clinicians cover and seal Laceraine gel under a transparent adhesive film dressing to avoid leakage of product from the intended site. This reduces risk of inadvertent spread of gel into eyes and mouths given the young age of many patients and the location of wounds about the head and face. Secondary retention bandage may also be used to maintain placement. This method does not require parents to hold the product in place as was described in some CTs. A clear retention dressing also enables limited visualisation of the wound during initial documentation and history assessments by the treating clinician. It allows for observation of tissue blanching that usually indicates effective response prior to commencement of procedures.

The proposed product information for Laceraine gel is based on the published CTs, and is consistent with the Australian ED guidelines. It is not expected that further mitigation is required.

2.5.5.8 Overdose and Dependence Potential

In the acute clinical setting, there is negligible risk of overdose. The absorption of the proposed combination product is pharmacologically limited by the vasoconstrictive effect of the adrenaline component of its formulation so that its effects are localised to the topical application site. Additionally, the viscosity of the dose form and method of administration make it difficult (if not impossible) to inject Laceraine gel, making high plasma levels associated with systemic absorption extremely unlikely (e.g. in comparison with possible unintended injection of topical solutions).

Furthermore, based on its localised, topical effect and very limited systemic absorption it is not expected to result in any central nervous system effects which would encourage abuse or lead to dependence.

2.5.5.9 Worldwide Marketing Experience

Worldwide experience with LAT gel and solution products is based on manufacture in hospital pharmacies. In Australia, s.47 [redacted] However, the gel is a recent development in the base formulation, so the growth of distribution sites nationwide of the previous solution formulation s.47 [redacted], indicate the high clinician confidence levels s.47 [redacted]

2.5.6 Benefits and Risks Conclusions

2.5.6.1 Benefits of Laceraine Gel

The combination of agents has been in use for many years with proven safety and efficacy. Additionally, the benefit of the complementary effects of local anaesthesia and vasoconstriction produces an ideal setting for painless wound cleaning, debridement, wound assessment and repair.

Our noted experience in using the gel is that improved coverage of gel formulation over the whole wound and margins, and improved retention over the wound without leakage of product has meant that the volume applied is often significantly less than 0.1mL /kg and provides improved efficacy of anaesthesia without the need for supplementary infiltration in most circumstances. It has been noted that signs of stinging, distress and withdrawal when gel makes contact with the wound are less frequently observed than with the liquid solution formulation, thereby improving effective application and retention with minimal distress. This contributes to the ease of safe local application and retention particularly in young children.

Storage and stability at ambient temperature facilitates timely application at initial point of care and contributes to efficient workflows in the ED. No refrigeration is required.

Clear benefits of Laceraine gel are: ease of application, improved visibility of the wound, decreased discomfort from a gel formulation and mitigation of risk in regard to retained dressing products, such as previously required for application of Laceraine solution, all of which deliver favourable outcomes.

The gel formulation is less likely to be applied incorrectly, which can result in inadequate anaesthesia (which may lead to reapplication), the need for local anaesthetic infiltration, possible procedural sedation in the ED or referral for general anaesthetic (GA) to undertake painful procedures. Procedural sedation and GA are largely safe and well tolerated but are time consuming and not devoid of rare but potentially serious complications. In circumstances where a wound requires surgical intervention, the gel facilitates early assessment and first aid measures such as irrigation and temporary dressing application to protect the wound and a reduced risk of subsequent infection whilst awaiting surgery.

There currently exists well established use and practice with Laceraine. A high degree of clinician confidence in efficacy has been noted over many years.

2.5.6.2 Risks Associated with Laceraine Gel

Overall, the risks associated with Laceraine solution have been mitigated with the increased viscosity of the gel. These were largely in relation to the potential for retained cotton wool/swab in the wound and greater likelihood of runoff into eyes and mouths.

An adhesive retention dressing retains the gel product over the intended location without the need for a cotton wool or other conduit. Improved containment over the wound means that any inadvertent application or leakage into eyes or mouth can be effectively managed with irrigation and is unlikely to carry systemic risks or adverse outcomes.

The tinted glass vial packaging requires complete removal of the seal, metal ring-pull collar and siliconized rubber bung to enable drawing up of the dose which is effectively limited to 3 mL due the viscosity of the gel and the inability to withdraw gel via a wide bore needle through the bung. Overdose or injection risk is mitigated.

2.5.6.3 Benefit - Risk Conclusion

Product efficacy, a high safety profile, expanded uptake nationally and strong clinical confidence since release of Laceraine s.47 , demonstrates that benefits far outweigh risks. When a single adverse case was reported in relation to application and removal technique, Phebra committed to significant product

development in collaboration with clinicians to mitigate risk and improve both utility and safety.

Regardless of whether used in distressed children or in anxious adults, the utility of Laceraine® Gel Topical Wound Anaesthetic has proven to be a very successful adjunct in the provision of safe, effective, timely acute wound care and demonstrably reduces pain and trauma that is often associated with wound management.

2.4 NONCLINICAL OVERVIEW

s.47

and now propose to register a topical dosage form -Laceraine® Gel Topical Wound Anaesthetic (Laceraine® Gel). Laceraine® Gel is a fixed dose combination product which contains:

- Lidocaine (lignocaine) hydrochloride monohydrate,
- Adrenaline (epinephrine) acid tartrate, and
- Tetracaine (amethocaine) hydrochloride

This combination of 2 local anaesthetic agents and a vasoconstrictor, which is abbreviated to LAT (or LET) in the published literature, has been well established with compounded solutions and gels available globally since the 1990s and the approval of a similar product by Medsafe in 2006 (Topicaine Solution, TT50-7343).

Laceraine® Gel is a new fixed combination in Australia and an OTC category N5 application has been prepared.

The Submission

The proposed indication for Laceraine® Gel Topical Wound Anaesthetic is for topical application to superficial wounds and lacerations to provide local surface anaesthesia for wound closure. It may be used to provide topical anaesthetic relief for cleaning, irrigation and debridement of painful minor wounds. The gel should only be used topically on broken skin.

This use follows current medical practice, that when patients (particularly children) present to an emergency department with injuries such as lacerations, a local, or topical, anaesthetic product is used to facilitate the cleaning of, and repair to, the wound. This practice is confirmed internationally by hospital guidelines, the published medical literature and is supported by a Cochrane review (Module 5.4).

The application is supported by Module 1, 2 (summaries), 3 (quality) dossier and a module 5 (clinical consisting of published studies identified by a systematic literature search performed in accordance with the TGA's literature based submission (LBS) guidelines). This application package does not contain a module 4 (nonclinical data).

The 3 active ingredients has been previously evaluated by TGA and is included either as a single medicine (one active ingredient) or in a fixed combination (more than one active) onto the Australian Register or Therapeutic Goods (ARTG for more than 10 years (Table 1) in the page 2. A similar fixed combination medicine with the same strength of actives is on the Medsafe register New Zealand since 2006 which satisfies the LBS requirement for established marketing history in an overseas country with comparable regulatory standards.

Table 1. Summary of first registration of actives on ARTG

Local anaesthetic AAN and [synonym]	Product name	Use	First approval	ARTG
lidocaine (lignocaine) hydrochloride monohydrate lidocaine [lignocaine, xylocaine] adrenaline (epinephrine) acid tartrate adrenaline (epinephrine)	ATO LIDOCAINE 2% lidocaine (lignocaine) And adrenaline (epinephrine) 2.2mL Injection cartridge	In combination with adrenaline, as local or regional anaesthetic and as nerve block for dental procedures and oral surgery	14 May 1998	63667
adrenaline (epinephrine) acid tartrate lidocaine (lignocaine) hydrochloride monohydrate	2% NUROCAIN DENTAL WITH ADRENALINE 1:100,000 2.2mL injection cartridge	Indications as on 17 July 2003: Lignocaine solutions are indicated for the production of local anaesthesia in routine dental procedures and oral surgery by means of infiltration and nerve block techniques. Lignocaine solutions with adrenaline are recommended for oral surgery requiring prolonged duration of anaesthesia and haemostasis.	31 Jul 1991	11963
adrenaline (epinephrine) acid tartrate lidocaine (lignocaine) hydrochloride monohydrate	2% XYLOCAINE DENTAL WITH ADRENALINE 1:80,000 2.2mL injection cartridge	Indications as at 25 July 2003: Lidocaine (lignocaine) solutions are indicated for the production of local anaesthesia in routine dental procedures and oral surgery by means of infiltration and nerve block techniques. Lidocaine (lignocaine) solutions with adrenaline (epinephrine) are recommended for oral surgery requiring prolonged duration of anaesthesia and haemostasis	13 Aug 1991	12024
tetracaine (amethocaine) hydrochloride tetracaine [amethocaine]	MINIMS tetracaine (amethocaine) hydrochloride 1.0% 10 mg/mL eye drops tube	Used as a local anaesthetic in the eye	30 Oct 1991	32254
	MINIMS tetracaine (amethocaine) hydrochloride 0.5% 5 mg/mL eye drops tube			32252

Phebra's proposed use of lidocaine in the Laceraine application/gel is within the approved indications (in Table 1), dose range and routes of administration.

Adrenaline has a wider use and features in many approved indications with a broad range of doses. In the treatment of cardiac arrest adrenaline is given at 0.1 mg/mL or 1 mg/mL subcutaneously or intramuscularly (or 0.1 mg/mL by very slow intravenous injection), while for anaphylaxis a dose of 300 µg (depending on body weight) is given intramuscularly usually by autoinjector. In dental use it is given by instillation or locally injected in the vicinity of a nerve truck 12.5 µg /mL (as a nerve block), and for surgical anaesthesia by epidural or as a nerve block 5 µg/mL.

In Australia tetracaine is approved for intra-optic/ophthalmic use as an eye drop in strengths 0.5% (5 mg/mL) and 1.0% (10 mg/mL). However, internationally tetracaine is used as a topical local anaesthetic in other settings (in the nose and throat, 2%) as well as parenterally (1% spinal anaesthesia: AHFS). The AHFS also specifically recommends its use with adrenaline (1%) to reduce the possibility of systemic absorption. Products combining tetracaine and lignocaine in creams (Pliaglis) and patches (Synera), for topical anaesthesia are also approved in international markets. Therefore, although its use in the proposed combination will constitute administration via a new route of administration (topically) in Australia, it has been widely used, and has been evaluated by other regulatory authorities for that route of administration, including Medsafe.

A more detailed justification for the particular combination is provided in module 1.5.6.

Nonclinical Development

The development of a pharmaceutical is a stepwise process involving an evaluation of both animal and human efficacy and safety information. The goals of the nonclinical safety evaluation generally include a characterisation of toxic effects with respect to target organs, dose dependence, relationship to exposure, and, when appropriate, potential reversibility.

This information is used to estimate an initial safe starting dose and dose range for the human trials and to identify parameters for clinical monitoring for potential adverse effects.

Once human clinical trials are conducted, and the pharmaceutical has been evaluated in-use through patient exposure over a sufficiently long duration (post authorisation) the non-clinical data becomes less relevant.

Individually the 3 active ingredients of Laceraine® Gel have been developed and marketed for decades. While the combination product (LAT) has not been formally licenced in many markets, it has been produced as a compounded speciality product and supplied to hospital pharmacies for at least 25 years in the UK and supplied under formal consent for over 15 years in New Zealand.

In Australia the combination of lidocaine and adrenaline (AUST R 63667) has been evaluated and registered since 1998, and Phebra's Laceraine® solution (the triple combination) was widely used from 2004-2020 (16 years) without any adverse drug reactions being reported.

Therefore, the goals of non-clinical safety evaluation have been essentially achieved, and Phebra does not propose to provide a Module 4. This decision was taken after conducting extensive literature searches for toxicology data on both the combination of active ingredients (LAT) and on the use of tetracaine in different route(s) of administration (than that registered). No relevant published literature was identified.

Aspects of the specific non-clinical studies routinely required for marketing authorisation of new pharmaceutical products have been considered. While tetracaine has not been registered for topical dermal application in Australia, the evaluation by Medsafe of Topicaine solution provides reassurance that the change to the route of administration (from intra-optical to topical/dermal) has not resulted in increased risk or toxicity from a patient's perspective.

Laceraine Gel Topical Wound Anaesthetic is presented in glass vials containing 4 mL of the application (gel) dosage form, for application in an emergency room or other acute care setting. Therefore, use is under the direction of health care professionals. Its use is essentially as a single 'dose' to a single patient. The topical application of this product contributes to a reduction in systemic exposure, which is further facilitated by the inclusion of the vasoconstricting agent (adrenaline), thus allowing application to open wounds without allowing the rapid absorption which could result in systemic toxicity. Therefore, the Sponsor believes the requirement of a further full toxicological evaluation of the combination is not be required.

A justification for the lack of nonclinical data is included with the nonclinical literature search rationale in the following pages. Phebra considers that the approach taken is sound and does not compromise on safety for patients.

Nonclinical Literature Search Rationale and Justification for the Absence of Module 4

The purpose of performing a non-clinical literature searches was to identify published data which would indicate studies of the toxicity of

(i) tetracaine in use/administration which was topical (but not ocular or ophthalmic – such use is approved), and

(ii) the proposed combination product lignocaine-adrenaline-tetracaine (LAT).

Searches were conducted by an experienced research librarian over the period 24-25 June 2021. The non-clinical search strategy (methodology) is provided in module 1.5.1.1.

The abstract of each search record was reviewed and categorised as either relevant or not relevant to the identification of evaluable toxicity data. The following categories were deemed to result in studies which were not relevant (and therefore excluded):

1. General exclusions:
    - Reviews
    - Letters to the editor, abstracts and conference papers
    - Duplicates identified in other searches
    - Languages other than English (unless the abstract in English identified potentially evaluable toxicity data.
2. Specific exclusions
    - Experimental or mechanistic studies (unless related to topical or dermal administration), including studies where tetracaine is used as a tool to examine calcium channels and membrane effects
    - Routes of administration other than topical or dermal
    - Use of tetracaine other than proposed use
    - Other combination products (not proposed formulation).

Table 2: Searches conducted for tetracaine (amethocaine) – route of administration other than ocular

Literature Search	Search ID	Number of records	Duplicates	Relevant
Tetracaine DART	Tet-1	19	0	0
Tetracaine acute toxicity Pubmed	Tet-2	6	0	0
Tetracaine acute toxicity Scopus	Tet-3	13	0	0
Tetracaine carcinogenicity Pubmed	Tet-4	16	0	0
Tetracaine carcinogenicity Scopus	Tet-5	12	1	0
Tetracaine carcinogenicity Toxline	Tet-6	7	7	0
Tetracaine local toxicity Pubmed	Tet-7	34	4	0
Tetracaine local toxicity Scopus	Tet-8	11	4	0
Tetracaine mutagenicity Pubmed	Tet-9	5	0	0
Tetracaine mutagenicity Scopus	Tet-10	7	3	0
Tetracaine mutagenicity Toxline	Tet-11	2	2	0
Tetracaine other toxicity Pubmed	Tet-12	16	13	0
Tetracaine other toxicity Scopus	Tet-13	31	17	0
Tetracaine preclinical PK Pubmed	Tet-14	24	11	0
Tetracaine preclinical PK Scopus	Tet-15	33	14	0
Tetracaine teratogenicity Pubmed	Tet-16	22	5	0
Tetracaine teratogenicity Scopus	Tet-17	6	1	0
Tetracaine topical in animals Toxline	Tet-18	35	29	0

Table 3: Searches conducted for the combination product (LAT)

Literature Search	Search ID	Number of records	Duplicates	Relevant
LAT Pubmed	LAT-1	11	0	0
LAT Toxline	LAT-2	13	0	0
LAT - animal pharmacokinetics Scopus	LAT-3	6	1	0
LAT – teratogenicity Scopus	LAT-4	9	1	0
LAT – toxicity Scopus	LAT-5	11	5	0

For the non-clinical searches the methodology is provided in Module 1.5.1.1 and the search outputs, provided with a tabulation of each search record (presented by search) and the results of the review and selection process in module 1.5.1.3.

None of the searches identified relevant studies of toxicity data for tetracaine or LAT.

Therefore, based on the lack of published literature to support either the topical (dermal) use of tetracaine or the toxicity of the proposed combination topical anaesthetic product, Phebra considers that the lack of Module 4, and consequently Module 2 Summaries, are justified.

The lack of published and evaluable non-clinical data is not considered a concern with regard to the toxicology of the proposed product, because of:

- the well established use of all 3 active ingredients over decades of use,
- the inclusion of each of the 3 active ingredients in products registered on the ARTG (although it is acknowledged that tetracaine has only been approved for topical use in the eye),
- the well established use of the combination of active ingredients, including approval of a solution (Topicaine Solution) in New Zealand since 2006, and

s.47

- The inclusion of the combination product, identified by the acronym ALA (amethocaine, lidocaine, adrenaline) in the Therapeutic Guidelines 2021.

It is therefore considered that the decades of clinical experience, supported by published clinical literature (Module 5), further remove the necessity for non-clinical data.

A justification for the fixed dose combination is provided in module 1.5.6.

Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Application no.: OM-2022-00069-1
e-Identifier: e006280 (0001)
Date: 11 July 2022

APPLICATION FOR REGISTRATION – CATEGORY 1
Evaluation of Microbiological Aspects

PRODUCT:	LACERAINE GEL TOPICAL WOUND ANAESTHETIC lidocaine HCl 40mg/mL + tetracaine (amethocaine) HCl 5mg/mL + adrenaline (epinephrine) acid tartrate 1.8mg/mL application vial
MANUFACTURER:	Phebra Pty Ltd 17-19 Orion Road Lane Cove West NSW 2145 Australia
SPONSOR:	Phebra Pty Ltd

In a letter dated 30 September 2021, the company has applied to register the new OTC medicine LACERAINE Gel Topical Wound Anaesthetic.

Laceraine Gel Topical Wound Anaesthetic is indicated for topical application to superficial wounds and lacerations to provide localised surface anaesthesia for wound closure. It may be used to provide topical anaesthetic relief for cleaning, irrigation and debridement of painful minor wounds.

The product is a fixed dose combination product containing:

- Lidocaine (lignocaine) hydrochloride monohydrate 42.66 mg/mL equivalent to lidocaine hydrochloride 40 mg/ml (4 % w/v)
- Tetracaine (amethocaine) hydrochloride 5.0 mg/mL (0.5 %w/v)
- Adrenaline (epinephrine) acid tartrate 1.8 mg/mL (0.18 % w/v)

The product is presented as a 4mL fill of 'semi-liquid application of moderate viscosity' (marketed as a gel) s.47 The product is a clear, colourless to straw-coloured, semi-liquid application. The listed excipients are sodium metabisulfite, hypromellose, and water for injections.

The product has a proposed shelf life of s. months when stored below 25°C.

s.47 MANUFACTURE

Description of Manufacturing Process

The proposed batch size is s.47 sufficient to fill approximately s.47

In a s.47 area, s.47 is placed into a vessel and s.47

A s.47 is removed, with an s.47 The company included s.47 in each of the s process validation batches, with acceptable s.47

The solution is s.47

Samples of s.47 , with an s.47 The company included a s.47

The filled vials are s.47

Following s.47 , samples are taken for s.47

s.47
The company has stated that s.47

Three s.47 have been conducted for the s.47

s.47 studies were undertaken concurrently.
s.47

s.47

The company has provided the following information s.47

s.47 [redacted]

The company has provided t s.47 [redacted]

s.47 [redacted]

Container Closure Integrity Testing

The company s.47 [redacted]

s.47 [redacted]

Sterility Testing

The company has stated that s.47 [redacted]

The company has stated that s.47 [redacted]

MICROBIOLOGICAL ASPECTS OF LABELLING

The company has provided copies of the proposed Product Information (PI), Consumer Medicine Information (CMI), carton and vial labels, which contain the following microbiologically significant statements:

Label Requirements

Vial Label	Laceraine Gel Topical Wound Anaesthetic lidocaine (lignocaine) hydrochloride 4 % w/v tetracaine (amethocaine) hydrochloride 0.5 %w/v adrenaline (epinephrine) acid tartrate 0.18 % w/v For topical application. For external use only Do not apply to mucous membranes. Store below 25°C. Do not refrigerate or freeze. Protect from light.
Carton Label	Laceraine Gel Topical Wound Anaesthetic lidocaine (lignocaine) hydrochloride 4 % w/v tetracaine (amethocaine) hydrochloride 0.5 %w/v adrenaline (epinephrine) acid tartrate 0.18 % w/v For external use only. Do not apply to mucous membranes. Contains no antimicrobial preservative. Store below 25°C. Do not refrigerate or freeze. Protect from light.

PI and CMI

PI

Under the heading <u>Method of Administration</u>

Laceraine Gel Topical Wound Anaesthetic contains no antimicrobial preservative. Use in one patient on one occasion only and discard any unused gel. Do not use if gel is discoloured or if the plastic cap is lifted or removed from the product.

Under the heading <u>Special Precautions for Storage</u>

Store below 25°C. Protect from light. Do not refrigerate or freeze.

CMI
Under the heading <u>Looking after your medicine</u>

Laceraine Gel Topical Wound Anaesthetic will be stored in the hospital, pharmacy or medical clinic.
Store below 25°C. Protect from light. Do not refrigerate or freeze.

The vial label, carton label and PI are acceptable from a microbiological perspective. The CMI is consistent with the PI.

RECOMMENDATIONS

The following questions should be put to the company and satisfactory responses received before approval for the application to register Laceraine Gel Topical Wound Anaesthetic is given:

s.47

2. Please provide details of the s.47
   Please also confirm that s.47

3. You have stated that s.47 testing is performed in accordance with s.47
   Please confirm that the s.47

Microbiology Section – Laboratories Branch
Therapeutic Goods Administration

Therapeutic Goods Administration
Complementary and OTC Medicines Branch
OTC Medicine Evaluation Section

LACERAINE GEL TOPICAL WOUND ANAESTHETIC vial

New/Varied OTC medicine

Evaluation of Presentation

Sponsor:	Phebra Pty Ltd
Submission ID:	OM-2022-00069-1
TRIM reference:	D23-5269220
eSubmission number:	e006280
Prepared by:	s.22
Date:	April 2023

	Quantity (mg/mL)	Role in formulation	Specification
Active Ingredients			
tetracaine (amethocaine) hydrochloride	5	Local anaesthetic	BP
lidocaine (lignocaine) hydrochloride*	40	Local anaesthetic	BP
adrenaline (epinephrine) acid tartrate	1.8	Vasoconstrictor	BP
Excipient Ingredients			
hypromellose	s.47	Thickening/gelling agent	BP
sodium metabisulfite	s	Antioxidant	BP
water for injections	s.	Diluent	BP

* Dossier indicates that it is added as (42.66 mg/ml) lidocaine hydrochloride monohydrate.

Sponsor's proposed indications:
Laceraine Gel Topical Wound Anaesthetic is indicated for topical application to superficial wounds and lacerations to provide localised surface anaesthesia for wound closure. It may be used to provide topical anaesthetic relief for cleaning, irrigation and debridement of painful minor wounds.

Requested shelf life:	Poisons schedule:
24 months when stored below 25°C.	S3

LACERAINE GEL TOPICAL WOUND ANAESTHETIC vial

Issues

1. **The product should be re-scheduled to S4.**
2. **Changes are required to labelling, PI and CMI**

This is a NEW PRODUCT application [application Level N5].

Background

This application is for registration of a new fixed-dose combination gel containing two local anaesthetics, lidocaine (lignocaine) hydrochloride and tetracaine (amethocaine) hydrochloride, combined with a vasoconstrictor adrenaline (epinephrine) acid tartrate.

Adrenaline is already combined with lidocaine in various registered injection anaesthetics (Xylocaine products). Adrenaline facilitates a local effect by vasoconstriction, reducing systemic absorption and providing a level of haemostasis. The only medicines containing tetracaine to have previously been approved in Australia are MINIMS tetracaine eye drops – AUST Rs 32252 and 32254, containing 0.5% and 1% tetracaine (amethocaine) hydrochloride respectively. Therefore, in addition to being a new fixed-dose combination, the proposed product constitutes a new topical route of administration for tetracaine.

Product background (from Clinical report)

The Sponsor's covering letter stated that Phebra was approached in 2003 by a number of facilities, including the Royal North Shore Hospital, Sydney, who were interested in using a combination local anaesthetic/vasoconstrictor product known in the literature as LAT (or LET). The LAT formulation contains a combination of lidocaine (lignocaine), adrenaline (epinephrine) and tetracaine (amethocaine). Phebra developed a sterile solution containing the LAT combination based on a sterile product produced by Torbay Pharmacy, South Devon Health Care, NHS Trust, United Kingdom (UK). The Torbay product (since reformulated to a gel, known as "LAT Sterile Gel") has been compounded and supplied to UK hospital pharmacies since 1995 and remains available on Torbay's current product listing (as an unapproved medicine). A similar LAT solution, Topicaine®, has been available as a commercial registered product in New Zealand. This product has been evaluated by Medsafe and consent for supply was granted on 21 December 2006.

s.47 The liquid solution supplied at the time required the use of cotton balls or swabs for application and retention over the wound. Depending on the location of the wound, and the age or compliance of the child, it was reported

that it was often difficult to retain the soaked dressing in place or to contain runoff. Therefore, a formulation that avoided the need to use Laceraine soaked cotton wool dressings was regarded as ideal.

Accordingly, Phebra developed a viscous application, known as Laceraine® Gel Topical Wound Anaesthetic, with the same active ingredients at the same concentrations as the liquid formulation. The new formulation is a semi-liquid and therefore the dose form is an application. However, Phebra propose to use the term "gel" in the product name. The product was manufactured in August 2020 and has been trialled at several hospitals, whose favourable response encouraged Phebra to cease manufacture of the solution and move to supplying only the semi-liquid application dosage form (gel) from early 2021.

Scheduling

The product currently falls in Schedule 3 of the Poisons Standard due to the presence of adrenaline, with the schedule 3 entry for adrenaline as follows:

> *ADRENALINE in preparations containing 1% or less of adrenaline **except** in preparations containing 0.02% or less of adrenaline unless packed and labelled for injection.*

The product falls under schedule 2 with respect to tetracaine and lidocaine, with the S2 schedule entries for these as follows:

> *TETRACAINE in preparations for topical use other than eye drops, containing 10% or less of total local anaesthetic substances **except** in dermal preparations containing 2% or less of total local anaesthetic substances.*
>
> *LIDOCAINE in preparations for topical use other than eye drops:*
> - *(a) containing 10% or less of total local anaesthetic substances, **except**:*
>   - *(i) in dermal preparations containing 2% or less of total local anaesthetic substances; or*
>   - *(ii)* in aqueous sprays for oromucosal use containing 0.6% or less of total local anaesthetic substances; or
> - *(b)* in divided preparations containing 200 mg or less of total local anaesthetic substances, **except** in lozenges containing 30 mg or less of total local anaesthetic substances per dosage unit.

The clinical evaluator has stated the following in relation to scheduling:

> It is recommended that consideration be given to scheduling Laceraine gel as a prescription only medicine rather than an OTC medicine. This medicine should only be used by medical or nurse practitioners for suturing lacerations. There are a number of significant contraindications that need to be taken into account when using the medicine. There are concerns that OTC availability has the potential for the medicine to be used inappropriately (e.g., burns, abrasions, leg ulcers, mouth ulcers, dog-bites, deep wounds, and wounds where vasoconstriction might result in ischaemia). It is noted that the authors of the PK study assessing lidocaine absorption from the intact skin under an occlusive dressing for 60 minutes in healthy volunteers recommended that "topical anesthetics - even OTC formulations - be used under the supervision of a healthcare professional to avoid adverse toxic effects and, in rare cases, death" (Oni 2012).

Further to the clinical evaluator's comments, non-prescription availability could perhaps lead to other inappropriate use such as for cosmetic procedures. In addition to numerous contraindications, the PI also notes that clinical caution is required in several circumstances (see 'Labelling' below). Finally, it is noted that experience with use of the proposed medicine has, to date, only been in controlled hospital settings.

For the above reasons, the product would be more appropriately scheduled as S4 and S3 scheduling would appear to be inappropriate. The matter will be referred to the Medicines Scheduling Secretariat with a recommendation to amend the Poisons Standard to restrict the product to Schedule 4.

Product name

There are no concerns with the product name. The ARTG name will be updated to include the container type – LACERAINE GEL TOPICAL WOUND ANAESTHETIC vial.

Indications

The requested ARTG indications are:

> "Laceraine Gel Topical Wound Anaesthetic is indicated for topical application to superficial wounds and lacerations to provide localised surface anaesthesia for wound closure. It may be used to provide topical anaesthetic relief for cleaning, irrigation and debridement of painful minor wounds.".

The clinical evaluator has recommended that the requested ARTG indications be accepted.

The requested label indications are:

> "Topical application for superficial local wounds and lacerations to provide local surface anaesthesia".

Directions for use

The clinical evaluator considered that the dose and directions for use, as specified in the PI, are supported by the submitted data. Dosage is as follows:

> *Children 1 to 3 years – 0.1 mL/kg to a maximum recommended dose of 2 mL*
> *Children over 3 years– 0.1 mL/kg to a maximum recommended dose of 3 mL*
> *Adults and adolescents – 0.5 mL per cm laceration to a maximum recommended dose of 3 mL.*

The carton label includes the following directions:

> *For dosage and contraindication information refer to the enclosed leaflet. Use in one patient on one occasion only and discard any unused product.*

The CMI, which is assumed to be included as the pack insert (to be confirmed; see CMI section below), includes general directions in terms of "*Your doctor or nurse will…*" and does not include

dosage. This would appear appropriate given the medicine should be applied by a doctor or nurse and reflects the consideration that the medicine should be scheduled as prescription-only (see Scheduling above).

There are no concerns regarding the directions for use.

Labelling

The applicant has provided colour mock-ups of the proposed labels.


Carton label


Vial label

Warning statements

The carton label includes the following RASML warnings required for both lidocaine- and tetracaine (amethocaine)-containing dermal products:

- Do not apply to large areas of the body, except on the advice of a healthcare practitioner.
- If skin irritation occurs, discontinue use and seek advice from your doctor or pharmacist.

Neither of the above RASML warnings is relevant or appropriate for this product and could be misleading or confusing as to use of the product. However (if the product were to remain in Schedule 3), a s14 exemption would be required to omit the warnings, given RASML warnings are a legal requirement (via TGO 92).

The label also includes the warnings "*For external use only. Do not apply to mucous membranes*" and a warning regarding the presence of sodium metabisulfite (required by TGO 92). However, several important contraindications are not included as warnings on the label, as follows:

- Do not use on the following:
  - fingers, toes, ears, penis or tip of the nose
  - burns
  - large or deep wounds, greater than 7 cm in length or involving deep structures such as bone, cartilage, tendon, nerve or major vessels (or on any sites where there is a possible entry to major veins or arteries)
  - contaminated wounds such as human or animal bites
- Do not use in children under 1 year of age
- Do not use if you have been treated with other local anaesthetics for pain relief or treatment for the current wound

The PI also refers to the need for "clinical caution" with the following:

- *Wounds adjacent to mucous membranes or eyes: protective precautions should be used to avoid leakage or rubbing into the eyes or mouth.*
- *Flap lacerations where vasoconstriction may potentially cause tissue ischaemia.*
- *Patients with epilepsy, asthma, hepatic impairment, complete heart block, impaired cardiac conduction, cardiovascular disorders, circulatory failure, hypovolaemia, shock, diabetes mellitus and peripheral vascular disease.*

- *If any adverse or systemic events are identified then the occlusive dressing should be immediately removed, the wound irrigated, and urgent clinical review obtained.*

Warnings regarding the above are included in the pack insert. If the product were to be an S3 medicine, a summary of the above warnings should be included on the label as follows, or similar:

> *Not suitable for serious wounds, burns, animal bites or for use on fingers or toes. Some situations may require extra caution. See the enclosed leaflet for further information, contraindications and warnings.*

Technically, there is no provision in TGO 92 for inclusion of the statement "Contains no antimicrobial preservative" in the consumer health information panel. However, this is likely to be included here to allay concerns regarding potential serious allergic reactions (eg. to chlorhexidine). Under the circumstances, this will not be pursued.

The container label is compliant with requirements. It is noted that the container is a glass vial that could potentially be mistaken for a vial for anaesthetic injection. The sponsor should comment on the potential risk of the product being mistakenly injected and whether further mitigation (eg label differentiation or other) might be appropriate.

The labelling otherwise complies with the requirements of TGO 92, SUSMP, RASML, ARGOM and the Therapeutic Goods Advertising Code.

Product information (PI) document

PI with sponsor justifications

The applicant should be asked to amend the PI as follows and provide the amended document for evaluation:

1. The document title should be amended to 'Australian Product Information' in accordance with formatting requirements.

2. The following correction should be made in the first paragraph of section 4.4: "*…should be strictly adhered to, to minimise the potential…*".

3. The list of *Contraindications relating* to "*wounds with end arteriolar supply due to vasoconstriction and risk of ischemia*" should include digits (fingers and toes) [as advised by the clinical evaluator].

   Digits have been excluded as a contraindication because two of the submitted studies specifically included patients with lacerations on the fingers and/or toes and in neither study was digital ischaemia reported as an adverse event: *White 2004* (fingers in 67 children and adolescents aged 5 to 18 years) and *Vandamme 2015* (finger/toes in 30 adult patients).

   However, standard clinical advice is that the use of local anaesthetics containing adrenaline should be avoided when repairing lacerations of the fingers or toes because of the potential risks of ischaemia due to vasoconstriction. *The Sydney Children's Hospitals Network*

guideline for the application of Laceraine in the ED includes the use of LAT gel as a contraindication for lacerations on the digits (i.e., *wounds with end arteriolar supply due to vasoconstriction and risk of ischaemia: includes digits, ear pinnae, tip of the nose and penis).* In addition, the PI for lidocaine (lignocaine) hydrochloride and lidocaine (lignocaine) hydrochloride and adrenaline (epinephrine) acid tartrate specifically contraindicates solutions with adrenaline for local analgesia in parts of the body with compromised blood supply or supplied by end arteries, such as fingers, toes, nose, ears or penis as there is a possibility of producing arterial vasoconstriction and subsequent ischaemic gangrene distal to the site of injection. In the context of what appears to be current standard Australian clinical practice for the use of local anaesthetics, it is recommended that Laceraine gel be contraindicated for wounds involving the digits.

4. The PI states '*No data available*' under '*Fertility, pregnancy and lactation*' and also under '*Genotoxicity'* and '*Carcinogenicity*'. Taking into account text available from other formulations of the active ingredients, the following text should be incorporated (as advised by Toxicology Section (D23-5325375):

Effects on fertility
No data available.

Use in pregnancy
Category A
The safe use of lidocaine (lignocaine) and/or tetracaine during pregnancy has not been established. Lidocaine (lignocaine) has however been used extensively for dental procedure during pregnancy with no proven increase in frequency of malformations or of harmful effects to mother or foetus.

Adrenaline has been given to 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 foetus having been observed. Adrenaline may delay the second stage of labour by inhibiting contractions of the uterus. Use with caution in pregnant women whose maternal blood pressure is in excess of 130/80.

Use in lactation
Lidocaine (lignocaine) passes into breast milk. The amount of lidocaine (lignocaine) appearing in breast milk from a nursing mother receiving parenteral lidocaine (lignocaine) is unlikely to lead to a significant accumulation of the parent drug in the breast-fed infant. The remote possibility of an idiosyncratic or allergic reaction in the breast-fed infant from lidocaine (lignocaine) remains to be determined.

It is not known whether tetracaine and/or its metabolites are excreted in milk. Safety for use in lactation has not been established.

Adrenaline is not orally bioavailable. Adrenaline is excreted in breast milk but would not be expected to have any effect on the nursing infant.

Genotoxicity
The genotoxic potential of 2,6-xylidine, a metabolite of lidocaine (lignocaine), has been studied with mixed results: Positive results were reported in assays for gene mutations (weakly positive in the Ames test with metabolic activation and in the mouse lymphoma assay) and chromosomal damage (chromosomal aberrations in Chinese hamster ovary cells at concentrations at which the drug precipitated from solution). No evidence of genotoxicity was found in in vivo assays for chromosomal damage (micronucleus assay) and DNA damage (unscheduled DNA synthesis). 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.

Tetracaine was not mutagenic in bacteria in limited studies. No studies to investigate the clastogenic potential of the drug have been performed.

Adrenaline and other catecholamines have been shown to have mutagenic potential in vitro and to be an oxidative mutagen in a WP2 bacterial reverse mutation assay. Adrenaline had a moderate degree of mutagenicity and was positive in the DNA Repair test with B. Subtilis (REC) assay but was not mutagenic in the Salmonella bacterial reverse mutation assay. Studies of adrenaline after repeated exposure in animals to evaluate the mutagenic potential have not been conducted.

Carcinogenicity
A two-year oral toxicity study of 2,6-xylidine, has shown that in both male and female rats, 2,6- xylidine in daily doses of 900 mg/m2 (150 mg/kg) resulted in carcinomas and adenomas of the nasal cavity. No nasal tumours were observed in the low dose (15 mg/kg or control animals). In addition, the compound also caused subcutaneous fibromas and or fibrosarcomas in male and female rats (significant at 150 mg/kg).

Studies have not been performed in either animals or humans to evaluate the carcinogenic potential of tetracaine.

Studies of adrenaline after repeated exposure in animals to evaluate the carcinogenic potential have not been conducted.

5. The clinical evaluator notes that while the PI states, under *Pharmacodynamic Properties; Clinical trials,* that no data are available, this is not correct — submitted published clinical trials indicate that the benefit-risk balance for LAT gel for the proposed usage is favourable.

   A brief summary of supporting clinical study data should be included under *Pharmacodynamic Properties; Clinical trials.* In this regard, the clinical evaluator has summarised the relevant efficacy outcomes from 13 provided clinical studies as follows:

   The submission included 13 studies providing satisfactory evidence of the efficacy of topical LAT for local anaesthesia for the repair of uncomplicated superficial lacerations of the skin in children, adolescents, and adults. The results from these 13 studies are summarised descriptively below:

   - *Three prospective, randomised, active-controlled, double-blind studies demonstrated the therapeutic equivalence of topical LAT compared with topical TAC for repair of superficial skin lacerations (Schilling 1995, Ernst 1995, and Ernst 1995b).*
   - *Three prospective, randomised, placebo-controlled, double-blind studies demonstrated therapeutic superiority of topical LAT compared with placebo for repair of superficial skin lacerations (Adler 1998, Harman 2013 and Priestley 2003).*
   - *One prospective, comparative, single-blind, intervention study demonstrated that LAT gel and LAT solution were similarly effective as topical anaesthesia for repair of uncomplicated lacerations of the face and scalp (Resch 1998).*
   - *Two observational studies provided supportive evidence for the efficacy of LAT gel for the repair of superficial skin lacerations (Vandamme 2015, White 2004).*
   - *Two prospective, randomised, controlled studies satisfactorily demonstrated the benefits of LAT compared with infiltrated local anaesthetic for repair of superficial*

skin lacerations (Ernst 1997, Lee 2012), as did one retrospective case series study (O'Connor 2010).

- *One, randomised, interventional, single-blind study demonstrated similar anaesthetic efficacy for LAT gel administered as a single-application or as three applications for repair of simple lacerations requiring suturing (Siembieda 2022).*

The above dot points could be included in the PI, prefaced with the following, or similar:

The safety and efficacy of topical LAT for local anaesthesia for the repair of uncomplicated superficial lacerations of the skin in children, adolescents, and adults is supported by the following:

6. The proposed PI should use consistent Australian spelling for "ischaemia" throughout the document.

Consumer medicine information (CMI) document

Proposed CMI

The product is to be supplied with a package insert, as referred to on the carton label. The applicant should confirm that the provided CMI is to be included as the package insert.

The applicant should be asked to amend the CMI/package insert as follows:

1. In Section 2:

   a. Under "Do not apply… if:", amend the fourth bullet point to "the wound is on a finger, toe, ear, the penis or the tip of nose~~, ears or penis~~ as it could affect the blood supply to these areas". This is in accordance with clinical evaluation and required amendment to the PI.

   b. Under "Be careful when applying … if:" amend the first bullet point to "the wound is very close to the eyes~~, or inside the nose, throat~~ or mouth. Protective measures should be used to avoid ~~irritation and side effects~~ leakage or rubbing into the eyes or mouth." This is consistent with the PI – the gel should not be used on mucous membranes.

2. In Section 7, reference to being available over-the counter may need to be revised if scheduling is revised to S4.

From: s.22
To: s.22
Subject: RE: OM-2022-00069-1; Request for Tox to evaluate Mod 4 aspects (justification for no Mod 4) [SEC=OFFICIAL]
Date: Tuesday, 25 April 2023 5:21:26 PM
Attachments: image001.gif
image002.png

Hi s.22

Since

- the combination of active ingredients Lidocaine (lignocaine) hydrochloride monohydrate, Tetracaine (amethocaine) hydrochloride and Adrenaline (epinephrine) acid tartrate has been used for several years overseas and in Australia (Laceraine® Topical Wound Anaesthetic),
- the application of the product will be of single use or sporadic nature, and by a medical professional,
- the clinical evaluator has accepted the lack of pharmacokinetics data,

the lack of local pharmacokinetics and local safety data is not considered a deficiency.

Taking into account that text is available from other formulations of the active ingredients, the following text should be incorporated to the Product Information document of **LACERAINE® Gel Topical Wound Anaesthetic**:

Effects on fertility
No data available.

Use in pregnancy
Category A
The safe use of lidocaine (lignocaine) and/or tetracaine during pregnancy has not been established. Lidocaine (lignocaine) has however been used extensively for dental procedure during pregnancy with no proven increase in frequency of malformations or of harmful effects to mother or foetus.

Adrenaline has been given to 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 foetus having been observed. Adrenaline may delay the second stage of labour by inhibiting contractions of the uterus. Use with caution in pregnant women whose maternal blood pressure is in excess of 130/80.

Use in lactation
Lidocaine (lignocaine) passes into breast milk. The amount of lidocaine (lignocaine) appearing in breast milk from a nursing mother receiving parenteral lidocaine (lignocaine) is unlikely to lead to a significant accumulation of the parent drug in the breast-fed infant. The remote possibility of an idiosyncratic or allergic reaction in the breast-fed infant from lidocaine (lignocaine) remains to be determined.

It is not known whether tetracaine and/or its metabolites are excreted in milk. Safety for use in lactation has not been established.

Adrenaline is not orally bioavailable. Adrenaline is excreted in breast milk but would not be expected to have any effect on the nursing infant.

Genotoxicity
The genotoxic potential of 2,6-xylidine, a metabolite of lidocaine (lignocaine), has been studied with mixed results: Positive results were reported in assays for gene mutations (weakly positive in the Ames test with metabolic activation and in the mouse lymphoma assay) and chromosomal damage (chromosomal aberrations in Chinese hamster ovary cells at concentrations at which the drug precipitated from solution). No evidence of genotoxicity was found in in vivo assays for chromosomal damage (micronucleus assay) and DNA damage (unscheduled DNA synthesis). 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.

Tetracaine was not mutagenic in bacteria in limited studies. No studies to investigate the clastogenic potential of the drug have been performed.

Adrenaline and other catecholamines have been shown to have mutagenic potential in vitro and to be an oxidative mutagen in a WP2 bacterial reverse mutation assay. Adrenaline had a moderate degree of mutagenicity and was positive in the DNA Repair test with B. Subtilis (REC) assay but was not mutagenic in the Salmonella bacterial reverse mutation assay. Studies of adrenaline after repeated exposure in animals to evaluate the mutagenic potential have not been conducted.

Carcinogenicity

A two-year oral toxicity study of 2,6-xylidine, has shown that in both male and female rats, 2,6- xylidine in daily doses of 900 mg/m2 (150 mg/kg) resulted in carcinomas and adenomas of the nasal cavity. No nasal tumours were observed in the low dose (15 mg/kg or control animals). In addition, the compound also caused subcutaneous fibromas and or fibrosarcomas in male and female rats (significant at 150 mg/kg).

Studies have not been performed in either animals or humans to evaluate the carcinogenic potential of tetracaine.

Studies of adrenaline after repeated exposure in animals to evaluate the carcinogenic potential have not been conducted.

Kind regards

s.22

Senior Toxicologist
Toxicology Section
Scientific Evaluation Branch
Therapeutic Goods Administration
Australian Government, Department of Health and Aged Care
Location: 27 Scherger drive, Fairbairn ACT
PO Box 100
Woden ACT 2606
www.tga.gov.au

The Department of Health acknowledges the traditional owners of country throughout Australia, and their continuing connection to land, sea and community.

From: s.22 @health.gov.au>
Sent: Friday, 21 April 2023 6:35 PM
To: TGA Toxicology s.22 @health.gov.au>
Subject: FW: OM-2022-00069-1; Request for Tox to evaluate Mod 4 aspects (justification for no Mod 4) [SEC=OFFICIAL]

Dear Tox

Sorry to ask so soon, but I'm wondering if you can give me an idea as to when the below OTC assessment might be completed. Unfortunately, it was sent to you very late in the process. I do appreciate that it needs to fit in with all the other work priorities of your Section.

While not ideal, I may send the first round request for information to the sponsor, advising that further request for information regarding toxicology aspects may still be forthcoming. But thought I'd check first in case the tox assessment might soon be available.

Many thanks
s.22

Senior Evaluator – OTC Medicines Evaluation Section
Complementary and OTC Medicines Branch

Medicines Regulation Division | Health Products Regulation Group
Australian Government, Department of Health and Aged Care
T: s.22 | E: s.22 @health.gov.au
Location: 27 Scherger Drive, Fairbairn
PO Box 100, Woden ACT 2606, Australia

From: s.22
Sent: Thursday, 30 March 2023 6:32 PM
To: TGA Toxicology s.22 @health.gov.au>
Cc: s.22 @health.gov.au>
Subject: OM-2022-00069-1; Request for Tox to evaluate Mod 4 aspects (justification for no Mod 4) [SEC=OFFICIAL]

Dear Toxicology

OTCMES request your evaluation of Mod 4 aspects (ie. assessment of justification for **no Mod 4 data**) for the OTC application OM-2022-00069-1; LACERAINE GEL TOPICAL WOUND ANAESTHETIC (e006280 (0001-) - Cover letter; application container E22-527454)

The application is for a new fixed-dose combination topical application product containing lidocaine + tetracaine + adrenaline, proposed for application to superficial wounds and lacerations to provide localised surface anaesthesia for wound closure and for cleaning, irrigation and debridement of painful minor wounds.

Tetracaine is currently only contained in Minims tetracaine (0.5% and 1%) eye drops, so the proposed product also constitutes a new route of administration for this active. It could perhaps also represent a new route of administration for adrenaline. However, as noted by the sponsor, the product has been used in s.47 for a number of years in Australia and the UK.

As indicated in the application cover letter, the Nonclinical Overview contains a justification for the absence of Module 4. It further states "Please note that the literature search on the non-clinical data pertaining to the active ingredients/formulation was performed. None of the literatures were found suitable. So, no information is provided in the module 4." (Search was

approved by IRRS - D22-5404092)

Clinical evaluation of the application has already been conducted (D23-5165197; report likely to be accepted as is) and the clinical evaluator has recommended approval. With respect to pharmacokinetics, the evaluator has stated "It is considered that the absence of PK data following administration of topical LAT gel for the proposed indication should not preclude registration of the product."

Product information

-

A proposed PI has been provided (e006280 (0001-) - PI) which appears to be mostly acceptable. It is noted that the PI states '*No data available*' under '*Fertility, pregnancy and lactation*' and also under '*Genotoxicity'* and '*Carcinogenicity*'. Presumably information on these is available and should be included (eg. from existing TGA-approved PIs). Could you please address this aspect also, indicating what we could ask the sponsor regarding provision of such information.

Regarding due date, unfortunately this is sent to you rather late in the evaluation process, so any chance of a somewhat hastened evaluation is appreciated.

Many thanks

s.22
Senior Evaluator – OTC Medicines Evaluation Section
Complementary and OTC Medicines Branch

Medicines Regulation Division | Health Products Regulation Group
Australian Government, Department of Health and Aged Care
T: s.22 | E: s.22 @health.gov.au
Location: 27 Scherger Drive, Fairbairn
PO Box 100, Woden ACT 2606, Australia

Australian Government

Department of Health and Aged Care

Therapeutic Goods Administration

Application no.: OM-2022-00069-1
e-Identifier: e006280 (0002)
Date: 23 August 2023

APPLICATION FOR REGISTRATION – CATEGORY 1

PRODUCT:	LACERAINE GEL TOPICAL WOUND ANAESTHETIC lidocaine HCl 40mg/mL + tetracaine (amethocaine) HCl 5mg/mL + adrenaline (epinephrine) acid tartrate 1.8mg/mL application vial
MANUFACTURER:	Phebra Pty Ltd 17-19 Orion Road Lane Cove West NSW 2145 Australia
SPONSOR:	Phebra Pty Ltd

In a letter dated 7 August 2023, the company has responded to the questions raised in the microbiological evaluation dated 11 July 2022.

1. A s.47 [redacted]

The company has stated that s.47 [redacted] and is acceptable.

2. Please provide details of s.47 [redacted] and confirm that the test method used for s.47 [redacted] Please also confirm s.47 [redacted]

The s.47 [redacted] which has been added to Section 3.2.P.2.5. A summary of the test method has been provided as follows:
s.47 [redacted]

PO Box 100 Woden ACT 2606 ABN 40 939 406 804
Phone: 1800 020 653 or 02 6289 4124 Fax: 02 6203 1605
Email: info@tga.gov.au https://www.tga.gov.au

s.47 [redacted]

This is acceptable.

3. You have stated that s.47 [redacted] is performed s.47 [redacted]
Please confirm that s.47 [redacted]

The company has confirmed that s.47 [redacted] is performed s.47 [redacted] This is acceptable.

RECOMMENDATIONS

There are no further objections from a microbiological perspective to the approval of the application.

Microbiology Section – Laboratories Branch
Therapeutic Goods Administration

Therapeutic Goods Administration
Complementary and OTC Medicines Branch
OTC Medicine Evaluation Section

Evaluation filenote

Product name: LACERAINE GEL TOPICAL WOUND ANAESTHETIC vial
Sub ID: OM-2022-00069-1
Application type: N5
TRIM No: D23-3176283
Prepared by: s.22
Date: 1 September 2023

Round 2 evaluation of non-Module 3 aspects (questions 1- 12)

Evaluation of sponsor response received 7 August 2023. Numbering corresponds to numbering in the s31 request.

Scheduling

1. The sponsor has responded in some detail to TGA's notification that the product will be referred to ACMS for consideration of scheduling. Notably, the sponsor has now included the statement "For Healthcare Professional Use Only" on the carton front panel. The response has been referred to the Scheduling Secretariat for inclusion in consideration of the scheduling (D23-2831550).

Labelling

2. The sponsor has agreed to remove the two non-relevant RASML warnings and seek s14 exemption. **This will need to be followed up closer to approval (ie request submission of exemption request and fees).**

3-4 Addressed. The labelling is acceptable (assuming scheduling remains S3).

Product information

5-10 All addressed except for question 6, which is a minor grammatical error, but correction will be again requested (ie. In Section 4.4, amend to "… should be strictly adhered to, to minimise…").

Other changes have been made to the PI as discussed below and further changes in relation to these are requested.

Additional precautions

These have been added regarding patients on MAOI, digoxin, quinidine or propranolol. The sponsor refers (in annotated version of revised PI) to s.47 documentation for Laceraine and the PI for Xylocaine, noting that while the former includes these as contraindications, these have been included as precautions in line with the Xylocaine PI (digoxin is not referred to at all in the Xylocaine PI). All are also referred to in the newly proposed Interactions section. Addition of theses as precautions is acceptable.

Medicine interactions

This section was essentially absent from the originally proposed PI and was not raised as an issue of concern in the clinical or labelling evaluations or the request for information. Nevertheless, the sponsor has commendably included interaction information drawn from the PI for Xylocaine and Xylocaine With Adrenalin (Aspen), with appropriate qualification regarding relevance to Laceraine included. Adrenaline interaction information has been included but most information regarding lidocaine interactions from the Xylocaine PI (also included in more recently approved PIs; eg. for AUST R 63667) has been excluded, with no explanation provided. It would appear appropriate to include further lidocaine interaction information also (noting the qualification regarding uncertainty as to relevance). Overall, the following amendments (in red/strikethrough) to the proposed interactions section should be requested, or omission justified:

The potential for interactions with other medicines is unknown.

Interaction related to systemic absorption (as a potential consequence of errors in dosing, method of application or route of administration) is uncertain. While no specific interaction studies have been performed for Laceraine and the absorption of anaesthetic agents with adrenaline from the skin is generally low, the following interactions have been noted for injectable or intravenously administered lidocaine and adrenaline.

The following interactions have been noted for injectable or IV lidocaine:

Anti-arrhythmic drugs: ~~*Local anaesthetics of the amide type, such as l*~~*Lidocaine (lignocaine)*~~*,*~~ *should be used with caution in patients receiving* ~~*other local anaesthetics or agents*~~ *structurally related* ~~*to amidetype local anaesthetics e.g. certain*~~ *anti arrhythmic drugs such as disopyramide, procainamide or*~~*,*~~ ~~*9*~~ *mexilitene since potentiation of cardiac effects may occur. Amiodarone has been reported to reduce the clearance of lidocaine (lignocaine).*

Beta adrenoreceptor antagonists~~*:*~~ ~~*such as p*~~*Propranolol and metoprolol reduce the metabolism of IV administered lidocaine (lignocaine) and the possibility of this effect with other beta adrenergic blockers should be kept in mind.*

Cimetidine: *Cimetidine reduces the clearance of IV administered lidocaine (lignocaine) and toxic effects due to high serum lidocaine (lignocaine) levels have been reported when these two drugs have been administered concurrently.*

Anticonvulsive agents: *Phenytoin and other antiepileptic drugs such as phenobarbitone, primidone and carbamazepine appear to enhance the metabolism of lidocaine (lignocaine) but the significance of this effect is not known. Phenytoin and lidocaine (lignocaine) have additive cardiac depressant effects.*

Inhalational anaesthetics: *Lidocaine (lignocaine) decreases the minimum effective concentration of inhalational anaesthetics, e.g. nitrous oxide.*

Skeletal muscle relaxants: *Lidocaine (lignocaine) and skeletal muscle relaxants, e.g. suxamethonium, lead to excessive neuromuscular blockade; therefore, this combination must be used with caution.*

Structurally related local anaesthetics: *Lidocaine (lignocaine) should be used with caution in patients receiving structurally related local anaesthetics.*

~~*In addition, t*~~*The following interactions* ~~*may occur with IV*~~ *have been noted for injected adrenaline (epinephrine) acid tartrate:*

... rest as per current.

CMI

11-12. Changes made as requested and additional, editorial-type changes are also acceptable.

Changes required to application form

- Amend product name to Laceraine~~®~~ Gel Topical Wound Anaesthetic vial
- Amend indications to "~~Laceraine Gel Topical Wound Anaesthetic is indicated f~~For topical application to..."
- Manufacturer details: s.47 [redacted]
- Shelf life – revise down to 18 months when stored below 25degC.
- Poisons schedule?!

Note: S14 exemption required for non-compliance with RASML requirements (see D23-5269220).

Australian Government

Department of Health and Aged Care

Therapeutic Goods Administration

Product:	Lidocaine + tetracaine + adrenaline gel (LACERAINE)
Sponsor:	Phebra Pty Ltd
Dose Form & Strength:	Gel, 4 mL (lidocaine 40 mg/mL, tetracaine HCl 5mg/mL, and adrenaline 1.8 mg/mL)
Submission No.:	OM-2022-00069-1
TRIM reference:	D23-4696219

To: s.22 , OTC

Toxicological advice on s.47 **in LACERAINE GEL TOPICAL WOUND ANAESTHETIC**

The Over-the-Counter section (OTC) has requested toxicological advice regarding the acceptability of s.47 in the proposed OTC product, LACERAINE GEL TOPICAL WOUND ANAESTHETIC.

The proposed OTC product, LACERAINE GEL TOPICAL WOUND ANAESTHETIC, contains the active ingredients tetracaine HCl, lidocaine HCl and adrenaline acid tartrate. The proposed indication is "*For topical application to superficial wounds and lacerations to provide localised surface anaesthesia for wound closure. It may be used to provide topical anaesthetic relief for cleaning, irrigation and debridement of painful minor wounds.*" The product is for single use and it is not intended for routine, repeated use.

The s.47 .

The Sponsor has justified the limit with the following arguments:

1. s.47

TGA comment:

The s.47 TGA agrees the route of administration is different.

The s.47

s.47 [redacted]

s.47 [redacted]

TGA Comment:

For s.47 [redacted]

s.47 [redacted]

TGA comment:

The safety s.47 [redacted]

Laceraine gel is presented as s.47 [redacted] The strength of Tetracaine (amethocaine) hydrochloride is 5.0 mg/mL (0.5% w/v). The proposed product information recommends a maximum dose of 3 mL, leading to the application of 15 mg of tetracaine for adults and adolescents. s.47 [redacted]

s.47 [redacted]

CONCLUSION

The proposed s.47 [redacted]

s.22 [redacted]
Toxicology Section
Scientific Evaluation Branch
22 December 2023

APPENDIX 1

Relevant documents provided by the sponsor or OTC section:

s.47

Therapeutic Goods Administration
Complementary and OTC Medicines Branch
OTC Medicine Evaluation Section

F i l e n o t e

Product name: LACERAINE Gel Topical Wound Anaesthetic
Sub ID: OM-2022-00069-1
Application type: N5
TRIM No: D24-946930
Prepared by: s.22
Date: 8 March 2024

The sponsor's response has been evaluated and outstanding matters have been resolved. While the shelf life of 4 months is very short, it will be accepted as discussed in Mod 3 evaluation report D23-5236669 and as discussed with s.22, Director OTCMES (5/3/24).

The product is effectively still the subject of ongoing consideration as to whether it should be up-scheduled to S4. The final decision on this matter is not expected until later in the year. The sponsor accepts that it may be up-scheduled but has nonetheless taken the commercial decision to go ahead with registration as an S3 medicine for now (see D23-3631636).

The product is legally required by TGO 92 to include RASML warning statements applying to lidocaine-containing dermal OTC medicines that contain more than 2% total local anaesthetic substances. However, these warnings are not appropriate for this medicine (see D23-5269220) so S14 exemption will be required for their omission from the label. The applicant will need to submit an '*Application for consent to import, supply or export goods that do not comply with standards - section 14/14A.*'

Sponsor verification of the provisional record is required. The following changes have been made:

- Product name amended to 'LACERAINE GEL TOPICAL WOUND ANAESTHETIC vial'
- Indications amended to "~~Laceraine Gel Topical Wound Anaesthetic is indicated f~~For topical application to…"

s.47

- Shelf life changed to 4 months when stored below 25°C