MEDSAFE

New Zealand Medicines and Medical Devices Safety Authority

Classification of lidocaine products intended for oromucosal use

Submission to the Medicines Classification Committee

Medsafe

September 2024

Introduction

Lidocaine is a local anaesthetic and causes loss of sensation (numbing) to any area of the body to which it is applied. It is also a type 1b antiarrhythmic agent [1].

Lidocaine may be used in many different clinical situations for example to relieve pain or to prevent pain related to procedures. Lidocaine may be administered via many different routes including injection, creams, gels, sprays and oral solutions [1,2].

Local anaesthetic systemic toxicity (LAST) is a potentially life-threatening adverse reaction affecting the central nervous and cardiovascular systems [3]. LAST is dose dependent; the risk is higher at elevated plasma concentrations normally associated with intravenous administration. However, cases of lidocaine toxicity have also been reported after accidental ingestion or overdose of oral gels and solutions in younger children and infants. Therefore, the most critical safety aspect of local anaesthetic therapy is appropriate dosing and administration [4,5].

Factors such as hepatic, renal or cardiac dysfunction can affect the metabolism of local anaesthetics. Younger children and infants are also at a higher risk of elevated levels due to low muscle mass, in addition to their immature hepatic metabolism [6].

At the 195th Medicines Adverse Reaction Committee (MARC) meeting, Medsafe sought advice from the MARC about the risk of toxicity of oromucosal lidocaine-containing products when used in younger children and infants. Oromucosal refers to medicines applied to mucosal areas within the mouth and upper gastrointestinal tract. Systemic absorption is possible when lidocaine is applied to oromucosal areas or via the gastrointestinal tract if swallowed [7,8].

Oromucosal lidocaine-containing products available for use in younger children and infants and are marketed for temporary relief of pain for infant teething, mouth ulcers, sore gums and other oral diseases and are available as general sale or through pharmacies (pharmacy-only classification) depending on strength of lidocaine in the product.

This topic was presented to the MARC following previous international regulatory authority safety communications which highlighted serious adverse reactions with use of oromucosal lidocaine in younger children and infants. Errors in administration and/or dosing, or accidental ingestion of oromucosal lidocaine products were identified as major contributing factors. The MARC were asked to review whether any regulatory action in New Zealand was needed to mitigate any potential risks of toxicity in this age group.

The Committee agreed that the risk of toxicity from oromucosal lidocaine products in younger children and infants was dose related. The Committee considered that the greatest risk of toxicity was due to accidental overdose or when package label instructions were not followed correctly. The Committee noted that some of the available products do not have maximum doses and/or have complicated dosing and administration instructions. The Committee also noted that the effectiveness of oromucosal lidocaine products for the management of teething was uncertain. Overall, the Committee highlighted a review of the labelling of oromucosal lidocaine-containing products and a review of the classification by the Medicines Classification Committee (MCC) was desirable.

The purpose of this submission to the MCC is to propose changes to the classification of lidocaine products containing 10% or less intended for oromucosal use in children under 12 years of age (with some exceptions further outlined in Part A). Two options are presented to the Committee for their discussion and consideration. Option 1 (preferred) proposes up-scheduling to the classification of restricted medicine, meaning that a pharmacist must be involved in the sale of the product. Option 2 proposes a pharmacy only classification and a label warning statement.

Consultation with a pharmacist reduces possible risks associated with medication errors and accidental ingestion in younger children and infants. Pharmacists can provide counselling to parents and caregivers about accurate dosing and administration and safe storage of the medicine. In addition, the pharmacist can check the person purchasing the product intends to use it for an appropriate purpose or if further medical advice is needed.

The MCC is also asked to consider whether mandatory label statements for oromucosal lidocaine-containing products are needed.

Part A- Regulatory Context and Proposed Classification

1. International non-proprietary (INN) name of the medicine

Lidocaine (lignocaine is the previous substance name). This report will use the INN lidocaine only.

2. Proprietary names (if applicable)

This report relates to the following lidocaine containing products only:

- **Lidocaine Gel 2%** (TT50-4388/1) (Orion Laboratories (NZ) Ltd c/o Pharmacy Retailing (NZ) Ltd t/a Healthcare Logistics)
- **Medijel Gel** (TT50-3967) (Wilson Foods Limited)
- **Xylocaine Jelly** (TT50-1937/6) (Pharmacy Retailing (NZ) Ltd t/a Healthcare Logistics)
- **Xylocaine Pump Spray** (TT50-1937/10) (Pharmacy Retailing (NZ) Ltd t/a Healthcare Logistics)
- **Xylocaine Viscous** (TT50-1937/32) (Pharmacy Retailing (NZ) Ltd t/a Healthcare Logistics)
- **Mucosoothe** (TT50-9726) (Orion Laboratories (NZ) Ltd c/o Pharmacy Retailing (NZ) Ltd t/a Healthcare Logistics).

3. Name and contact details of the company/ organisation/ individual requesting a reclassification

Pharmacovigilance Team, Clinical Risk Management, Medsafe
Email: medsafeadrquery@health.govt.nz

4. Dose form(s) and strength(s) for which a change is sought (if applicable)

Table 1: Dose forms and strengths of lidocaine-containing products intended for oromucosal use which a change is sought

Proprietary name	Dose form	Strength of lidocaine	Pack size
Lidocaine Gel 2%	Topical gel	2% w/w	20g
Medijel Gel	Topical gel	0.66%	15g
Xylocaine Jelly	Topical gel	2% w/v	30mL
Xylocaine Pump Spray	Oral spray	10%	50mL
Xylocaine Viscous	Oral solution	2% w/v	200mL
Mucosoothe	Oral topical gel	2% w/v	200mL

Source: Medsafe Product/Application search: www.medsafe.govt.nz/regulatory/dbsearch.asp (4 September 2024)

Change is sought for the classification of external use medicines containing lidocaine that are intended for oromucosal use in children under 12 years of age (except for throat lozenges and except throat sprays that contain lidocaine 2% or less).

It is not proposed that this change will affect lidocaine containing products applied to the surface of the skin or other mucosal areas. These products were not reviewed as part of the report presented to the MARC.

Current approved products relevant to this report are outlined above in Table 1 above. All of these products are approved for use in adults and children. More information about these products is outlined in Part B of this report.

Please refer to Section 7 (present classification of the medicine) for further information.

5. Pack size, storage conditions and other qualifications (if applicable)

Pack sizes of approved oromucosal products containing lidocaine range from 15-20 g and 30-200 mL for topical gels and 50 mL pack size for an oral spray.
There are no special storage requirements for these products (e.g., all products require storage at or below 25 or 30°C).

6. Indications for which change is sought (if applicable)

Not applicable.

7. Present classification of the medicine

Summary of present classification

Table 2 outlines the current classification of lidocaine. Classification relevant to this submission have been highlighted.

Table 3 provides examples of approved lidocaine-containing products that are either pharmacy only or general sale medicines. Products that are discussed in this report are highlighted in yellow.

A history of the MCC's consideration of lidocaine can be found attached in **Appendix A.**

Table 2: Classification of lidocaine in New Zealand *(classification relevant to this submission are highlighted)*

Classification	Conditions (if any)
Prescription	for injection **except** when used as a local anaesthetic in practice by a nurse whose scope of practice permits the performance of general nursing functions or by a podiatrist registered with the Podiatry Board or by a dental therapist, oral health therapist or dental hygienist (without local anaesthetic exclusion on their scope of practice) registered with the Dental Council; **except** when containing 2.5% or less and used topically as a local anaesthetic in practice by a dental therapist, oral health therapist or dental hygienist (without local anaesthetic exclusion on their scope of practice) registered with the Dental Council; for ophthalmic use **except** when used in practice by an optometrist registered with the Optometrists and Dispensing Opticians Board; for oral use **except** in throat lozenges in medicines containing 30 milligrams or less per dose form; for external use in medicines containing more than 10%; **except** in throat sprays in medicines containing 2% or less; **except** when specified elsewhere in this schedule.
Pharmacy-only	for urethral use; for external use in medicines containing 10% or less and more than 2%
General sale	in throat lozenges in medicines containing 30 milligrams or less per dose form; for external use in medicines containing 2% or less; in throat sprays in medicines containing 2% or less

Source: Classification Database: www.medsafe.govt.nz/profs/class/classintro.asp (4 September 2024).

Table 3: Examples of lidocaine-containing products, pharmacy only or general sale classification (*products included in this submission are highlighted*).

Product name	Active ingredients (strength of lidocaine)	Classification
Throat lozenge		
Difflam Plus anaesthetic + antibacterial + anti-inflammatory lozenge	Benzydamine + dichlorobenzyl alcohol + lidocaine (4mg/lozenge)	General sale
Medix Anaesthetic Lozenge	Benzydamine + dichlorobenzyl alcohol + lidocaine (4mg/lozenge)	General sale
Strepsils anaesthetic lozenge	Amylmetacresol + dichlorobenzyl alcohol + lidocaine (10mg/lozenge)	General sale
Throat spray		
Difflam Plus Sore throat Spray	Benzydamine + dichlorobenzyl alcohol + lidocaine (559mcg/spray)	General sale
Strepsils Plus anaesthetic spray	Amylmetacresol + dichlorobenzyl alcohol + lidocaine (780mcg/spray)	General sale
Oral spray		
Xylocaine Pump	Lidocaine (10%)	Pharmacy only
Oral solution		
Xylocaine Viscous	Lidocaine (2%)	Pharmacy only
Oral topical gel		
Mucosoothe	Lidocaine (2%)	Pharmacy only
Topical gel		
Instillagel	Chlorhexidine + lidocaine (19.6ml/mL)	Pharmacy only
Instillagel Lido	Lidocaine (20mg/g)	Pharmacy only
Lidocaine Gel 2%	Lidocaine (2%)	General sale[a]
Medijel Gel	Aminoacridine + lidocaine (0.66%)	General sale[a]
Soov Bite gel	Cetrimide + lidocaine (3%)	Pharmacy only
Xylocaine jelly	Lidocaine (2%)	Pharmacy only
Topical spray		
Soov Burn topical spray	Cetrimide + lidocaine (2%)	General sale
Topical cream		
Emla topical cream	Lidocaine (2.5%) + prilocaine	Pharmacy only
LMX4 topical cream	Lidocaine (4%)	Pharmacy only
Numit topical cream	Lidocaine (2.5%) + prilocaine	Pharmacy only
Soov topical cream	Cetrimide + chlorhexidine + lidocaine (1%)	General sale
Virasolve topical cream	Benzalkonium chloride + idoxuridine + lidocaine (2%)	General sale
Dermal patch		
Emla dermal patch	Lidocaine (2.5%) + prilocaine	Pharmacy only
Topical solution		
Topicaine topical solution	Adrenaline + lidocaine (4%) + tetracaine	Restricted
Nasal spray		
Entop Plus nasal spray	Lidocaine (50mg/mL) + phenylephrine	Pharmacy only

a. These medicines are currently presented as pharmacy only medicines.

Source: Medsafe Product/Application search: www.medsafe.govt.nz/regulatory/dbsearch.asp (4 September 2024). Not all approved products are listed.

8. Classification sought

This submission proposes changes to the classification of lidocaine containing medicines intended for oromucosal use in children under 12 years of age (except for throat lozenges and except throat sprays 2% or less).

As described in the Introduction and Part B of this submission, a key safety concern identified by the MARC was the risk of lidocaine toxicity in younger children and infants due to medication errors, incorrect use or accidental overdose of oromucosal lidocaine-containing products in this age group. Oromucosal lidocaine products relevant to this submission are approved in adults and children.

Two options for changes to classification are proposed to the Committee (see also Table 4).

Option 1 - Restricted classification (preferred)

Add a new restricted classification.

Restricted: *For external use in medicines containing 10% or less for oromucosal use, except for use in adults and children 12 years of age and over, (except throat lozenges, except throat sprays 2% or less).*

The statement means that throat lozenges and throat sprays 2% or less can still be used in children under 12 years of age because they remain general sale medicines. This change would mean that oromucosal gels, solutions and sprays containing lidocaine 10% or less, in children under 12 years of age would be restricted. This removes the pharmacy only products for oromucosal use and general sale products for oromucosal use for children under 12 years of age.

Since this is an additional statement, oromucosal lidocaine gels, solutions and sprays for adults and children over 12 years of age containing between 2 – 10% would remain pharmacy only medicines and 2% or less remain as general sale medicines

This classification would satisfy the MARC recommendation.

While younger children and infants (< 3 years of age) are more susceptible to possible toxicity relating to medication error or accidental ingestion with oromucosal lidocaine containing products, on review of the indications, dose and administration instructions of current products available, input from a pharmacist for use in children under 12 years of age would be beneficial (see also Part B).

As per the current classification, all external use medicines containing more than 10% lidocaine remain prescription medicines.

Restricted medicines require a data sheet. This means that information relating to possible toxicity when the medicine is administered incorrectly and risks of accidental

overdose in younger children and infants will be available for healthcare professionals, who will be able to inform parents and caregivers. This is particularly important for use of lidocaine 2% viscous/oral solution (discussed further in Part B).

Several products such as Xylocaine Pump spray, Xylocaine Jelly and Xylocaine Viscous solution currently have published data sheets.

Purchasing restricted medicines requires interaction with a pharmacist, which provides oversight for larger pack sizes of oromucosal lidocaine, and the pharmacist can give advice as to suitability of the product, dosing to reduce the risk of medication errors in children and safe storage advice.

Option 2 – Pharmacy only (not preferred)

An alternative option is add a new pharmacy only classification.

Pharmacy only*: For external use in medicines containing 10% or less for oromucosal use, except in adults and children over 12 years of age, (except throat lozenges, except throat sprays 2% or less).*

The statement means that throat lozenges and throat sprays 2% or less can still be used in children under 12 years of age because they remain general sales medicine. This change would mean that oromucosal gels, solutions and sprays containing lidocaine 10% or less, in children under 12 years of age would be pharmacy only. This removes general sale products for oromucosal use in children under 12 years of age.

Since this is an additional statement, oromucosal lidocaine gels, solutions and sprays for adults and children over 12 years of age containing more than 2% and less than 10% would remain pharmacy only medicines and 2% or less remain as general sale medicines

Both restricted and pharmacy only medicines must be sold from a pharmacy. The two key differences between a restricted (pharmacist-only) classification and pharmacy only classification are:

1. An interaction with a pharmacist is not required. This lessens the opportunity to help mitigate some of the risks identified for these products when used in younger children and infants.

2. A datasheet is not required for a pharmacy only medicine. The lessens the information that is available to healthcare professionals and consumers about use in younger children and infants.

An appropriate warning statement for use of oromucosal lidocaine medicines could mitigate some risk of this classification. For example - *Do not use in children under 12 years of age except on the advice of a healthcare professional.*

Option 2 harmonises more closely to the Australian classification. Lidocaine in Australia is available as Schedule 5, Schedule 4 (prescription), Schedule 2 (pharmacy-only), or is unscheduled (available at general sales) [9]. The classification of lidocaine in Australia is as follows:

Schedule 4 (Prescription): Lidocaine ***except*** *(a) when included in Schedule 2 or 5 or (b) in dermal preparations containing 2% or less of total anaesthetic substances per dosage unit or (c) in lozenges containing 30 mg or less of total anaesthetic substances per dosage unit.*

Schedule 2 (Pharmacy-only): Lidocaine in preparations for topical use other than eye drops: ***(a)*** *containing 10% or less of total local anaesthetic,* ***except:*** *(i) in dermal preparations containing 2% or less of total anaesthetic substances or (ii) in aqueous sprays for oromucosal use containing 0.6% or less of total anaesthetic substances or*

(b) *in divided preparations containing 200 mg or less of total anaesthetic substances, except in lozenges containing 30 mg or less of total anaesthetic substance per dosage unit.*

In Australia, lidocaine oromucosal gels and solutions 10% or less are pharmacy only. In contrast, in New Zealand, lidocaine oromucosal gels and solutions are classified as pharmacy only medicines more than 2% and less than 10%, and general sale when 2% or less.

The Committee should consider whether any changes to the lidocaine classification for oromucosal use should harmonise with that of Australia.

Impact on other existing classification statements

A limit of 10% lidocaine is proposed in the restricted or pharmacy only classification statement; this is in line with the current classification of external use lidocaine concentrations not requiring consultation with a doctor and reduces the need for changes to current available products.

Table 5 (below) shows current approved and available products for which a change in classification is sought and potential changes to classification. All of the relevant products discussed in this report are approved for both adults and children.

Oromucosal lidocaine products used in adults and children 12 years of age and over, are not proposed to be affected by proposed changes. However, products included in this submission are approved for both adults and children.

For both classification change proposals, products for external use that are not intended for oromucosal use, throat lozenges and throat sprays under 2% would not be affected. This includes topical gels containing lidocaine for urethral use, such as for catheterisation and products that are applied to the surface of the skin.

However, the changes proposed may however impact products with a range of indications, ages for use and methods of administration.

Table 4: Proposed classification of lidocaine

Classification	Conditions (if any)
Prescription	for injection **except** when used as a local anaesthetic in practice by a nurse whose scope of practice permits the performance of general nursing functions or by a podiatrist registered with the Podiatry Board or by a dental therapist, oral health therapist or dental hygienist (without local anaesthetic exclusion on their scope of practice) registered with the Dental Council; **except** when containing 2.5% or less and used topically as a local anaesthetic in practice by a dental therapist, oral health therapist or dental hygienist (without local anaesthetic exclusion on their scope of practice) registered with the Dental Council; for ophthalmic use **except** when used in practice by an optometrist registered with the Optometrists and Dispensing Opticians Board; for oral use; for external use in medicines containing more than 10%; **except** in throat sprays in medicines containing 2% or less; **except** in throat lozenges in medicines containing 30 milligrams or less per dose form; **except** when specified elsewhere in this schedule.
Restricted	For external use in medicines containing 10% or less for oromucosal use, except for use in adults and children 12 years of age and over, (except throat lozenges, except throat sprays 2% or less) (**Option 1 – Preferred**)
Pharmacy-only	for urethral use; for external use in medicines containing 10% or less and more than 2% For external use in medicines containing 10% or less for oromucosal use, except for use in adults and children 12 years and over (except throat lozenges, except throat sprays 2% or less) **(Option 2)**
General sale	in throat lozenges in medicines containing 30 milligrams or less per dose form; for external use in medicines containing 2% or less in throat sprays in medicines containing 2% or less;

Table 5: Current and proposed classification of oromucosal lidocaine containing products only approved and available in New Zealand

Proprietary name	Dose form (strength)	Current classification	Proposed classification as per current product information (Option 1 - preferred)	Proposed classification as per current product information (Option 2)
Lidocaine Gel 2%	Topical Gel 20g (2%)	General sale	Restricted	Pharmacy only
Medijel Gel	Topical Gel 15g (0.66%)	General sale	Restricted	Pharmacy only
Xylocaine Jelly	Topical Gel 30 mL (2%)	Pharmacy-only	Restricted	Pharmacy only
Xylocaine Pump spray	Oral spray 50 mL (10%, 10 mg/ spray dose)	Pharmacy-only	Restricted	Pharmacy only
Xylocaine Viscous	Oral solution 200 mL (2%)	Pharmacy-only	Restricted	Pharmacy only
Mucosoothe	Oral topical gel 200 mL (2%)	Pharmacy-only	Restricted	Pharmacy only

Source: Medsafe Product/Application search: www.medsafe.govt.nz/regulatory/dbsearch.asp (4 September 2024).

9. Classification status in other countries (especially Australia, UK, USA and Canada), and any justification for harmonisation

Australia [9]

As mentioned above, oromucosal lidocaine gels and solutions containing less than 10% of lidocaine are pharmacy only medicines. Similar products to New Zealand are available in Australia, such as Xylocaine Jelly, Mucosoothe and Xylocaine Viscous, which are pharmacy only.

United Kingdom [10]

Oromucosal lidocaine gels and solutions in the United Kingdom (UK) are available at general sale or pharmacy only. These products are indicated for mouth ulcers, denture irritation and/or infant teething.

Products used for infant teething (including with other indications) must contain less than 1% lidocaine and are pharmacy-only. These products can be used in infants from 5 months of age.

Products that are not indicated for infant teething are available as general sale or pharmacy only. A higher strength gel containing 2% lidocaine (in combination with other medicines) is a pharmacy only medicine and is not for use in children under 12 years of age.

Xylocaine Pump spray (10%) is a pharmacy only medicine in the UK and has similar indications to Xylocaine Pump Spray in New Zealand.

Refer to Part B for further information.

Note: In the UK products which are 'pharmacy only' can only be bought from a pharmacy and in the presence of a pharmacist. 'Pharmacy only' medicines in the UK are not usually displayed on open shelves. In this way pharmacy only medicines in the UK are similar to New Zealand restricted medicines [11].

10. Extent of usage in New Zealand and elsewhere (e.g. sales volume) and dates of the original consent to distribute

There is a long history of use of lidocaine containing oromucosal medicines in New Zealand, with some products having been supplied before 1969 with grandfathered approval under the current legislation (highlighted below).

Approval date of lidocaine containing oromucosal medicines:

- Medijel Gel: 8 September 1988
- Lignocaine Gel 2%: 17 December 1987
- Xylocaine Jelly: 31 December 1969
- Xylocaine Viscous: 22 May 1997
- Xylocaine Pump Spray: 31 December 1969
- Mucosoothe: 5 May 2016

11. Local data or special considerations relating to New Zealand (if applicable)

Data from the New Zealand National Poisons Centre is discussed in Part B of this submission.

12. Labelling or draft labelling for the proposed new presentation(s) (if applicable)

There are no specific labelling considerations (other than possible warning statements) related to this submission.

13. Proposed warning statements (if applicable)

Table 6: Current warning statements on applicable products

Proprietary name	Warning information on package label
Lidocaine Gel 2%	• Use only on medical advice • Do not eat or drink within 60 minutes of using the gel in the mouth or throat area • Absorption from mucous membranes is relatively high, excess gel should be removed • If irritation occurs, stop use immediately and seek medical advice • Contains hydroxybenzoates[a] • Not to be used for teething pain
Medijel Gel	• Do not use in infants under 6 months of age • For infant teething disorders, avoid excess and prolonged treatment • If symptoms persist , consult your doctor or dentist • Contains alcohol 10% w/w, saccharin and sugars[a]
Xylocaine Jelly[b]	• Do not eat or drink within 60 minutes of using Xylocaine Jelly within mouth or throat area. • Use only on medical advice • Absorption from mucous membranes is relatively high, excess Xylocaine Jelly should be removed. • Contains hydroxybenzoates[a]
Xylocaine Pump spray[b]	• Contains alcohol (ethanol 24.1% w/v) and saccharin[a] • Do not eat or drink within 60 minutes of administration to the mouth or throat • For professional use only • Xylocaine Pump Spray is designed to provide surface anaesthesia of mucous membranes • Extreme care should be exercised if endotracheal procedures are envisaged since the nozzle may become detached from the plastic cap • Absorption from wound surfaces and mucous membranes is relatively high • Xylocaine Spray should be used with caution in patients with traumatised mucosa and/or sepsis in the region of the proposed application • Avoid contact with eyes • Do not cut or shorten nozzle • Nozzles should not be reused and should be discarded immediately after use • Do not use the same nozzle on different patients. Additional short nozzles are available separately. • The number of sprays used will depend on the extent of the area to be anaesthetised • Your healthcare professional will use the dose that is suitable for you.
Xylocaine Viscous[b]	• Do not eat or drink within 60 minutes of use • Contains hydroxybenzoates and saccharin[a] • Children (under 3 years): Not for teething pain.

Mucosoothe	• Do not eat or drink within 60 minutes of use • Not to be used for teething pain • Contains hydroxybenzoates[a] • Contains 189 mg of sodium per 120 mL (maximum recommended daily dose)[a]

a. Label statements are required as per the Medsafe Label Statement Database due to presence of related excipients in the drug product and are not related to the lidocaine.
b. Published data sheet available: www.medsafe.govt.nz/Medicines/infoSearch.asp

Source: Medsafe Evaluation Filing (September 2023).

Lidocaine warning statements

There are currently no mandatory warning statements specifically relating to lidocaine containing medicines in New Zealand as outlined in the Label Statements Database (LSD). Although a number of approved products containing lidocaine in New Zealand do carry warning statements (see Table 6 above).

In Australia the following label statements are required for lidocaine containing medicines [12].

Lidocaine (Lignocaine) *(Entry 1 of 4)*	In dermal preparations containing MORE THAN 2% of total local anaesthetic substances	• 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.
Lidocaine (Lignocaine) *(Entry 2 of 4)*	In dermal preparations containing 2% OR LESS of total local anaesthetic substances	• If skin irritation occurs, discontinue use and seek advice from your doctor or pharmacist.
Lidocaine (Lignocaine) *(Entry 3 of 4)*	In preparations for topical oral use containing more than 1.5% lidocaine.	• Do not use for teething pain in children.
Lidocaine (Lignocaine) *(Entry 4 of 4)*	In lozenges	• Do not take hot food or drink if the mouth feels numb after taking this product as it may burn the mouth. • Do not give to children under 6 years of age, unless recommended by a doctor, pharmacist or dentist.

It is noted that in Australia topical oral preparations (i.e. those for oral mucosal use) containing more than 1.5% lidocaine must have the label statement 'Do not use for teething pain in children'.

Comparison with choline salicylate

At the 66th Medicines Classification Committee (MCC) meeting, on the 11 May 2021, the MCC reviewed the classification and warning statements for choline salicylate. Choline salicylate is a medicine used for relief of pain caused by mouth ulcers or teething [13].

The MCC recommended that the warning statements for choline salicylate be updated (Medsafe 2021). The LSD requires the following warning statements for medicines containing choline salicylate (Medsafe Label Statement Database 2024).

Substance/Group/Class	Conditions	Statements or requirements
Choline salicylate	When sold as a general sales medicine	• Do not use in infants under 18 months of age. • Do not use in patients known to be allergic to salicylate. • Do not exceed the maximum stated dose. • Prolonged or excessive use can be harmful.
	When sold as a Pharmacy-only medicine	• Do not use in babies under 4 months of age. • Do not use in patients known to be allergic to salicylate. • Do not exceed the maximum stated dose. • Prolonged or excessive use can be harmful.

MCC to consider lidocaine warning statements

The MCC are asked to consider if mandatory warning labels are needed on products discussed in this report, such as warnings statements relating to excessive and/or prolonged use, or maximum doses.

Recommended warning statements

Do not exceed the maximum stated dose.

Prolonged or excessive use can be harmful.

*Do not use in children under 12 years of age except on the advice of a healthcare professional. (*This statement is recommended if the MCC recommends a classification change to pharmacy only).

14. Other products containing the same active ingredient(s) which would be affected by the proposed change

This submission affects all lidocaine containing medicines intended for oromucosal use in children under 12 years of age (except throat lozenges and except throat sprays 2% or less).

This submission does not affect throat lozenges, throat sprays under 2%, lidocaine containing products that are used on the skin (such as creams, topical gels and patches) or other mucous membranes (such as the urethra) or in the eye. However, the changes proposed may however impact products with a range of indications, ages for use and methods of administration.

Please also refer to Table 3 above.

Part B- Clinical Context and Implications

15. Safety concern

Lidocaine toxicity

Local anaesthetic systemic toxicity (LAST) is a potentially life-threatening adverse reaction that may occur at high plasma concentrations of local anaesthetics, including lidocaine [3].

LAST is dose dependent and the risk is higher at elevated plasma concentrations, such as when lidocaine is administered intravenously [3].

LAST events often start with signs and symptoms of CNS excitation (e.g. perioral numbness, metallic taste, mental status changes or anxiety, visual changes, muscle twitching and seizures), followed by CNS depression (e.g. somnolence, coma and respiratory depression) [3].

Younger children and infants are more susceptible to lidocaine toxicity. This age group are at a higher risk of elevated anaesthetic plasma levels due to low muscle mass, in addition to immature hepatic metabolism [6].

Lidocaine-containing gels, viscous oral solutions or sprays are administered to the oral mucosa for temporary relief of pain. Systemic absorption from these products is possible through absorption of the mucosal or via the gastrointestinal tract if swallowed [7,8].

When lidocaine is applied to the oral mucosa, the rate of systemic absorption and amount of dose absorbed is dependent upon the concentration and total amount administered, as well as the specific site of application and duration of exposure. Additional absorption may occur if the surface epithelium in the region of proposed application is damaged [2,8,14].

If lidocaine is swallowed, it undergoes extensive first pass hepatic metabolism before being systemically absorbed. The bioavailability of ingested lidocaine is about 35% [8].

Lidocaine toxicity in younger children and infants with oromucosal use

International regulatory authority safety communications have highlighted reports of serious adverse reactions related to lidocaine toxicity with use of oromucosal lidocaine-containing products in younger children and infants [5,15].

Seizures have been reported in association with of lidocaine viscous 2% administered to paediatric patients. A review by the FDA highlighted reports of

toxicity, including seizures, severe brain injury and cardiovascular problems, with lidocaine viscous 2% solution administered to children aged 5 months to 3.5 years. The majority of the reports noted administrative errors, using higher doses than prescribed, and accidental ingestion [5].

The risk of toxicity in younger children and infants due to lidocaine oral gels/solutions may be caused by difficulties in dose calculation and administration of these products in this age group [16].

The risk of ingestion of lidocaine-containing products applied to the oral mucosa may be higher if the child is crying, drooling, or salivating. It may be hard to determine the amount of lidocaine administered to the child as it quicky becomes mixed with saliva and may be spat out or swallowed [16].

In New Zealand, the Xylocaine Viscous (lidocaine 2%) data sheet includes a warning relating to use in paediatric patients. This warning states that post-marketing cases of seizures, cardiopulmonary arrest, and death in patients under the age of 3 years have been reported with use of Xylocaine Viscous when it was not administered in strict adherence to the dosing and administration recommendations [2].

Children who have ingested lignocaine-containing solutions/gels or other topical lidocaine preparations require hospital assessment if doses over >6 mg/kg are ingested or if there are symptoms. Early clinical features include agitation, confusion, disorientation, and drowsiness [17].

Summary

There have been reports of serious adverse reactions in younger children and infants following the use of lidocaine 2% oral solution. Most of these reactions occurred when the medicine was not administered correctly or in cases of overdose.

Incorrect use or accidental ingestion of oromucosal lidocaine products in younger children and infants increases the risk of toxicity. Therefore, implementation of appropriate risk minimisation measures should reduce these risks.

At the 195th Medicines Adverse Reaction Committee (MARC) meeting, Medsafe sought advice from the MARC about the risk of toxicity of oromucosal lidocaine-containing products when used in younger children and infants. The MARC were asked to review whether any regulatory action was needed to mitigate any potential risks of toxicity. Products that were discussed in the report are currently pharmacy only or general sale medicines.

The Committee agreed that the risk of toxicity from oromucosal lidocaine products in younger children and infants was dose related. The greatest risk of toxicity was due to accidental overdose or when package label instructions were not followed correctly.

The Committee recommended that oromucosal lidocaine products be referred to the MCC to review the classification of oromucosal lidocaine products and consider whether mandatory label statements are needed.

The report presented to the MARC is available on the Medsafe website.

The minutes of the meeting are available on the Medsafe website.

16. Indications

Table 7: Indications of products where reclassification is sought

Product name (current classification)	Age for use	Indication
Medijel Gel (General sale)	Adults and children over 6 months of age	*Package label*: Quick and effective relief from the pain of mouth ulcers, soreness of the gums, denture rubbing and infant teething.
Xylocaine Viscous (Pharmacy only)	No age limit on package label	*Package label:* Temporary relief of pain and discomfort associated with: irritated or inflamed mucous membranes of the mouth, pharynx and upper gastrointestinal tract; introduction of instruments and catheters into the respiratory and gastrointestinal tract. *Data sheet:* Indicated for the relief of pain and discomfort associated with irritated or inflamed mucous membranes of the mouth, pharynx and upper gastrointestinal tract e.g. post-tonsillectomy sore throat, dumping syndrome; introduction of instruments and catheters into the respiratory and gastrointestinal tract.
Mucosoothe (Pharmacy only)	No age limit on package label	*Package label:* Indicated for the relied of pain and discomfort of mucous membranes of the mouth, throat and upper gastrointestinal tract.
Lidocaine Gel 2% (General sale)	No age limit on package label.	*Package label:* For topical anaesthesia and anaesthesia of mucous membranes where lubrication is required.
Xylocaine Jelly (Pharmacy only)	No age limit on package label.	*Package label:* For anaesthesia of mucous membranes where lubrication is required. Topical anaesthesia of the urethra. For pain relief after circumcision in children. *Data sheet:* Indicated as a surface anaesthetic and lubricant for the male and female urethra during cystoscopy, catheterisation, exploration by sound and other endo-urethral procedures; nasal and pharyngeal cavities in endoscopic procedures such as gastroscopy and bronchoscopy; during proctoscopy and rectoscopy; tracheal intubation. To relieve pain after circumcision in children.
Xylocaine Pump Spray (Pharmacy only)	Adults and children > 3 years of age	*Package label:* Topical anaesthetic for mucous membranes. *Data sheet*: For the prevention of pain associated with the following procedures: • *Otorhinolaryngology:* Puncture of the maxillary sinus and minor surgical procedures in the oral and nasal cavity, pharynx and epipharynx. • *Obstetrics*: During the final stages of delivery and before episiotomy and perineal suturing as supplementary pain control. • Introduction of instruments, tubes and catheters into the respiratory and digestive tract: • *Dental practice*: Before injections, dental impressions, X-ray photography, removal of calculus.

Source: Medsafe evaluation filing and data sheets and consumer medicine information (accessed August 2023)

Lidocaine containing products used for application to the mucosa of the mouth and throat are typically used to provide local anaesthesia to these areas. This may be for temporary relief of pain from oral conditions or to prevent pain relating to procedures or introduction of instruments into the upper respiratory tract or gastrointestinal tract [1,2].

Table 7 (above) outlines the indications for the applicable products discussed in this report. As mentioned in Part A, as per the current classification these products are available without input from a healthcare professional.

In infants and children, parents or caregivers may use lidocaine containing products to manage pain relating to inflammation of the gums, teething, mouth ulcers or sore throats.

Medijel Gel is currently the only product containing lidocaine approved for use in infant teething in NZ. There is a warning on the package label of Lidocaine Gel 2%, Xylocaine Viscous and Mucosoothe to not use for infant teething.

There are no age limits for use on the package labels for Lidocaine Gel 2%, Xylocaine Viscous, Mucosoothe and Xylocaine Jelly.

While not legally required, a published data sheet is available for Xylocaine Viscous which contains additional information about use in younger children and infants. Section 4.4 of the data sheet includes that use of the product in patients less than 3 years of age should be limited to those situations where safer alternatives are not available or have been tried but failed due to safety concerns when not administrated in strict adherence to dosing and administration recommendations. This information is not on the package label of Xylocaine Viscous or Mucosoothe.

A published data sheet is also available for Xylocaine Jelly and Xylocaine Pump Spray.

Lidocaine Gel 2% is indicated for topical anaesthesia and anaesthesia of the mucous membranes where lubrication is required. The package label does not specifically state the location of use for topical anaesthesia, which is noted on the package labels for Mucosoothe and Xylocaine Viscous.

Excluding Medijel Gel, the indication for use for oromucosal lidocaine containing products include for use relating to procedures or in dentistry.

Xylocaine Pump Spray 10% (oral spray) is indicated for the prevention of pain associated with the procedures including in otorhinolaryngology, obstetrics, dental practice and introduction of instruments tubes and catheters into the respiratory and digestive tract. The product may be used in children aged between 3 – 12 years of age. The package label states that less concentrated lidocaine solutions are recommended in children under 3 years of age. The package label includes the statement ‘for professional use only’.

Appropriateness of self-selection of applicable products in children under 12 years

Infant teething

The appropriateness of use of lidocaine for teething without healthcare professional input has been highlighted noting that the use of lidocaine in infant teething is not recommended by some guidelines (NICE guidelines and American Academy of Paediatrics recommendations) [18,19].

In some countries lidocaine-containing products for infant teething are not available (e.g., Australia, Canada) or have undergone review to improve the risk benefit balance (e.g., UK). In the UK, lidocaine-containing products for infant teething require pharmacist consultation and are second-line treatment after non-pharmacological treatment [18].

Other inflammatory conditions of mouth, throat and/or gums

Oromucosal conditions in younger children and infants may relate to underlying medical conditions and may require medical input. Painful inflammation of the oral mucosa may reduce fluid intake and lead to dehydration [20, 21, 22].

The indication for use as a topical anaesthetic for Lidocaine Gel 2% is very broad. There are no current warnings on the package label that do not recommend its use on the oral mucosa, however, use of oral gels such as Mucosoothe or Xylocaine Viscous may be more likely preferred.

Additional advice on whether use of a lidocaine-containing product for treatment of oral inflammation is appropriate would be beneficial for parents and caregivers.

Use in procedures

Some oromucosal lidocaine products have indications for use in procedures and therefore would be administered by or under the supervision of a healthcare professional, likely in a hospital setting on a one-off occasion, particularly use of Xylocaine Pump Spray 10%.

Side effects

The Xylocaine Viscous data sheet outlines important safety information for use in paediatric patients. To reduce the risk of serious adverse events, healthcare

professionals should instruct parents and caregivers to strictly adhere to the prescribed dose and frequency of administration and store the bottle safety out of reach of children [2].

This safety information can be extrapolated to other oromucosal lidocaine containing products. As the risk of toxicity is dose dependent, potential risks are higher with products containing higher strengths of lidocaine.

A consumer is unlikely to read the data sheet, if there is one, to find out more information about risks of use in children under 3 years of age. Pharmacy medicines are not legally required to have a data sheet.

Having a healthcare professional to inform parents and caregivers of these risks and appropriate use of the product is desirable.

Age of use

The majority of applicable products do not have an age at which use is indicated.

The Xylocaine Viscous data sheet recommends that use in children less than 3 years of age should be limited to those situations where safer alternatives are not available or have been tried but failed. As there is a dosing recommendation for this age group stated on the package, the impression may be that the product is safe to use as first line treatment. Mucosoothe, while a generic of Xylocaine Viscous, does not have a data sheet.

A consumer cannot be expected to identify alternative treatment options, and therefore further discussions with a healthcare professional are needed.

17. Dose

Table 8: Dose and administration instructions of products where classification change is sought

Product name (current classification)	Directions for use	Dose and frequency
Medijel Gel (General sale)	Apply a small quantity of Medijel to the painful area.	Repeat the application after 20 minutes if necessary. Same as adults (children > 6 months of age)
Xylocaine Viscous (Pharmacy only)	*Mouth:* swish the solution for 30 seconds and spit out. *Throat:* the solution should be gargled and may be swallowed.	• Adults: Up to 15 mL, no more than 120 mL per day. Not more often than every 3 hours. • Children over 3 years of age: up to 4 mg/kg or 5mL whichever is lower. No more than 4 doses in 24 hours. Not more often than every 3 hours. • Children under 3 years of age: up to 4 mg/kg or 1.25 mL whichever is lower. Apply with a cotton swab. No more than 4 doses in 24 hours. Not more often than every 3 hours. *Additional information from data sheet*: in children over 3 years of age, it is recommended that excess solution is spat out. There is not enough documentation to allow recommendations for a more prolonged use of Xylocaine Viscous in children under 3 years of age.
Mucosoothe (Pharmacy only)	*Mouth:* swish the gel for 30 seconds and then spit out. *Upper gastrointestinal tract and throat*: the gel should be gargled and may be swallowed.	• Adults: Up to 15mL, no more than 120mL. Not more often that every 3 hours. • Children 3 – 12 years of age: No more than 4mg/Kg (0.2mL/Lg) of bodyweight or 5mL (100mg lidocaine hydrochloride) whichever is lower. No more than 4 doses in 24 hours. Not more often that every 3 hours. • Children under 3 years: No more than 4mg/Kg (0.2mL/Kg) of bodyweight or 1.25ml (25mg of lidocaine hydrochloride) whichever is lower, accurately measured and applied only to the affected area with a cotton swab. No more than 4 doses in 24 hours. Not more often that every 3 hours.
Lidocaine Gel 2% (General sale)	Apply a thin layer as needed or as directed by your healthcare professional.	• Adult and children > 12 years: Endoscopy – up to 20g. Lubrication of endotracheal intubation – 2g to the surface of the tube. Maximum dose: No more than 30mL of gel should be given in any 12-hour period. • Children under 12 years of age: up to 6mg/Kg can be used.
Xylocaine Jelly (Pharmacy only)	Additional information on instructions per indication in the data sheet.	• Adults and children > 12 years: Urethral anaesthesia: Male 20g, Female 5 – 10g. Endoscopy: up to 20g. Lubrication for endotracheal intubation: 2g to the surface of the tube • Children under 12 years: Up to 6mg/Kg can be used.

Xylocaine Pump Spray (Pharmacy only)	Additional information on instructions per indication in the data sheet.	The number of sprays used will depend on the extent of the area to be anaesthetised. • Adults: Dental practice: 1 – 5 sprays to mucous membranes. Puncture of the maxillary sinus (cavity of the upper jaw) or other minor surgical procedures: 3 sprays. Obstetrics – during delivery: up to 20 sprays. • Introduction of instruments and catheters into respiratory and digestive tract: up to 20 sprays. During prolonged procedures up to 40 sprays. • Children 3 – 12 years: Do not exceed 3mg/Kg of bodyweight of lidocaine. Reduced to 1.5mg/Kg bodyweight of lidocaine when used in the larynx or trachea. • Children less than 3 years: Less concentrated lidocaine solutions are recommended. *Additional information from data sheet*: The dosage recommendations should be regarded as a guide. The clinician's experience and knowledge of the patients physical status are of importance in calculating the required dose.

Source: Medsafe evaluation filing and data sheets and consumer medicine information (accessed August 2023).

Table 8 (above) outlines the dose and administration instructions for the applicable products discussed in this report.

Risks for lidocaine toxicity in children under 12 years of age

Medijel Gel

Dose and administration: Directions for use may increase the risk of excessive use or accidental overdose due to frequent application (every 20 minutes). There is no recommended maximum daily dose, nor size of dose to administer on the package label.

The risk of toxicity with Medijel may be less likely due to a lower concentration of lidocaine (0.66%) versus other products.

Other: The size of the tube is 15g (6.6mg/g, 99mg of lidocaine).

Mucosoothe, Xylocaine Viscous

Dose calculation: Dose calculation is required for use in children based on weight. Once this dose is calculated, if this dose is lower than 100mg lidocaine (children 3 – 12 years) or 25mg (under 3 years), then this is the dose to be administered. There may be a possibility of dose calculation error. Caregivers and parents may require assistance in assuring the correct dose for the child is used if the medicines

are purchased over the counter, in addition to use of a measuring device if applicable.

Frequency for use: The package label for Mucosoothe and the data sheet for Xylocaine Viscous include maximum of 4 doses per 24 hours for children. This information is not on the package label of Xylocaine Viscous.

Duration of use: There are currently no warnings on the package labelling relating to duration of use. Section 4.2 of the Xylocaine Viscous data sheet includes that there is not enough documentation to allow recommendation for a more prolonged use in children under the age of 3 years.

Warnings: There are limitations to the amount of information that can be included on a package label. Important information about serious adverse reactions in children, important of accurate dosing and administration, and consideration of alternative therapies, are important risk minimisation measures for toxicity.

While not required to have a data sheet, the Xylocaine Viscous data sheet contains this important information, which can be used by healthcare professionals when providing education to parents and caregivers.

Administration instructions: When used for anaesthesia of the mouth, the oral gel is swished in the mouth and then spat out. However, the gel may be swallowed for anaesthesia for the upper gastrointestinal tract and throat. In children less than 3 years of age, it is recommended that the oral gel is accurately measured and applied only to the affected area with a cotton swab. The Xylocaine Viscous data sheet includes that in children over 3 years of age, excess solution is recommended to be spat out.

Other: Mucosoothe and Xylocaine Viscous are 200 mL bottles (20mg/mL = 4,000mg lidocaine). These products have a child resistant cap.

Lidocaine Gel 2%, Xylocaine Jelly

Dose and directions for use: In children under the age of 12 years a dose of up to 6mg/Kg is recommended. This is a higher dose in comparison to Xylocaine Viscous and Mucosoothe (4mg/Kg).

The dosing recommendations are the same for younger children to that of older children (i.e., over 3 years old versus less than 3 years old).

There is no additional information on how to administer the product to children provided, including frequency of applications or maximum daily dose.

Other: Lidocaine Gel 2% is a 20g tube. Xylocaine Jelly is a 30g tube.

Xylocaine Pump Spray 10%

Dose calculation: In children aged between 3 – 12 years of age the recommended dose as per the package label is maximum of 3mg/Kg of lidocaine, reduced to 1.5mg/Kg when used in the larynx or trachea. The dose would therefore need to be calculated into corresponding number of sprays (1 spray = 10mg of lidocaine) per bodyweight.

As per the package label, this product should be administered by healthcare professionals only.

Other: The spray bottle in 50mL and contains 500 doses (5000mg of lidocaine).

Summary

For medicines that are sold without the input of a healthcare professional, consumers must be able to obtain information from the product package label and/or package insert (if available) to be informed how to use the product correctly.

Dosing and administration instructions of the available oromucosal lidocaine containing products are complex and may pose an increased risk of toxicity from medication error.

Review of the package labelling of oromucosal lidocaine-containing products identified possible areas where the risk of overdose and/or medication errors may be increased. This included calculation of dose based on weight, specific administration instructions in younger children, lack of information about frequency and/or maximum doses. It was also noted that none of the products included information about risks of serious adverse reactions that may occur in younger children and infants on the package label if the product was used incorrectly or if accidental ingestion occurred.

Prolonged and/or excessive use is also a risk factor for overdose. Some product labels do not have information about how long to use the product or clear instructions for frequency of use. While some conditions such as a mouth ulcer may be acute and self-limiting. Other conditions, such as infant teething, may

occur over a longer period of time. Application of teething gels may also be over a wider area of mucosa.

The MARC discussed that the greatest risk of toxicity from oromucosal lidocaine-containing products when used in younger children and infants was due to accidental overdose or when package label instructions where not followed correctly.

A pharmacist can counsel parents and caregivers about how to use these products appropriately, including dosing and administration information, and duration of use. In addition, to check that the indication sought for the product is appropriate and does not warrant further medical advice. Information on safe storage of the medicine could also be provided.

18. Overdose and medication errors

There have been reports of medication error, cases of accidental exposure and suspected overdose in children with oromucosal lidocaine containing products internationally [5].

New Zealand Poisons Centre

As part of the report presented to the MARC, the New Zealand Poisons Centre (NPC) was asked to review exposures to specific products with lidocaine from 2018 – 2023, in children under the age of 3 years.

A total of 9 exposures were identified within the time period, and all were ingestions. Further information about the cases is outlined in Figure 1.

Figure 1: Exposures to specific lidocaine products in human patients

Patient age in years	Year	Reason	Product	Amount ingested	Dose mg/kg
0	2018	Therapeutic error	[redacted]	~1g of gel	3.1
3	2019	Therapeutic error		~3ml of gel	3.3
0	2020	Child exploratory		Half a tube (7.5g)	4.4
3	2020	Child exploratory		"Small amount"	Below INCR
2	2020	Child exploratory		~5g of gel	**6.7****
1	2020	Child exploratory		~2.5ml of gel	4.2
1	2023*	Child exploratory		~14g (almost a whole tube)	**8.1****
3	2023*	Child exploratory		~13g (almost a whole tube)	**6.1****
1	2023*	Child exploratory		15g (whole tube)	**7.6****

INCR = intervention criteria; a limit where a patient will likely be sent in for medical assessment. This includes reaching an ingested dose of 6 mg/kg in the case of ingestions of lidocaine. *January-June included in search for cases. **Above INCR.

A total of 4 patients ingested at least half a tube of a product, and 4 patients reached the intervention criteria level (referral to medical assessment) of 6mg/Kg

lidocaine ingested. All patients were asymptomatic at the time of contact with the NPC.

They may be additional reports of excess exposure of lidocaine oral gels in children in NZ that have not been reported to the NPC.

The reports highlight the importance of keeping medicine away from younger children.

The reports may highlight that oral lidocaine products are being used in infants. However, it is not known if the product was intended for the child or another person.

19. Overseas information

Australia

Mucosoothe and Xylocaine Viscous are available in Australia and are pharmacy only medicines. The products have similar labelling, indications, dosing, and warnings to NZ data sheet.

Xylocaine 2% Jelly is also a pharmacy only medicine, that has similar indications, dosing, and administration instructions to the NZ product.

United Kingdom

Oromucosal lidocaine-containing products (gels or solutions) for infant teething, mouth ulcers and denture irritation are available in the UK.

Table 9 outlines examples of oromucosal lidocaine-containing products in the UK and the classification.

Products that are indicated for infant teething must contain less than 1% lidocaine and are pharmacy only (require input with a pharmacist).

Xylocaine Pump Spray (10%) is a pharmacy only medicine in the UK and has similar indications to Xylocaine Pump Spray in New Zealand.

Except for Xylocaine Pump Spray, lidocaine oromucosal gels and solutions in the UK as pharmacy only or general sale medicines are for specific conditions in the mouth. This is different to some products in New Zealand which may cover a range of indications.

Table 9: Examples of oral lidocaine-containing products available in the UK, by product name, indication and directions for use

Product name	Ingredients	Indication	Directions for use
Infant teething gels			
Anbesol Teething gel *(Pharmacy only)*	Lidocaine hydrochloride 1%, chlorocresol 0.1%, cetylpyridinium chloride 0.02%	Relief of pain and discomfort associated with teething in children from 5 months of age, where non-pharmacological treatments have failed to provide sufficient relief.	Apply a pea-sized amount (0.2 grams) with a clean finger to the affected area of the gum. The dose may be repeated if necessary after 3 hours, up to a maximum of 6 doses in 24 hours.
Calgel Teething gel *(Pharmacy only)*	Lidocaine hydrochloride monohydrate 0.33%, cetylpyridinium chloride 0.1%	For relief of pain and discomfort associated with teething in children from 5 months of age, where non-pharmacological treatments have failed to provide sufficient relief	Apply a pea-sized amount (0.2 grams) with a clean finger to the affected area of gum. The dose may be repeated if necessary after 3 hours, up to a maximum of 6 doses in 24 hours
Mouth ulcers, sore gums etc +/- infant teething			
Anbesol liquid *(Pharmacy only)*	Lidocaine hydrochloride 0.9%, chorocresol 0.1%, cetylpyridinium 0.02%	Adults, the elderly and children: for the temporary relief of pain caused by recurrent mouth ulcers and denture irritation. In children from 5 months of age: For relief of pain and discomfort associated with teething where non-pharmacological treatments have failed to provide sufficient relief.	*Adults and the elderly:* Apply to the affected area, a small undiluted amount of Anbesol Liquid, by covering the bottle mouth with a clean fingertip, inverting once and returning the bottle to the upright position. Two applications immediately will normally be sufficient to obtain pain relief. The application may be repeated if necessary after 3 hours. *Babies teething and children:* apply to the affected area 0.25mL of undiluted liquid by covering the bottle mouth with a clean fingertip, inverting once and retuning the bottle to the upright position The

			application may be repeated if necessary after three hours, up to a maximum of 6 doses in 24 hours.
Bonjela Junior Gel *(General sale)*	Lidocaine 0.5%, cetylpyridinium chloride 0.025%	For the relief of pain from common mouth ulcers and denture irritation	Adults, the elderly, and children over 5 months: apply a little gel to the sore area with either a clean finger or swab. This may be repeated after twenty minutes then every 3 hours.
Medijel Gel *(General sale)*	Lidocaine hydrochloride 0.66%, aminoacridine hydrochloride 0.05%	Relief from the pain of common mouth ulcers and denture rubbing	Apply to the affected area with a clean finger or small pad of cotton wool. If necessary application may be repeated after 20 minutes. Each dose is approximately 2mg of lidocaine.
Anbesol Adult Strength Gel *(Pharmacy only)*	Lidocaine hydrochloride 2%, chlorocresol 0.1%, cetylpyridinium chloride 0.02%	For the temporary relief of pain caused by recurrent mouth ulcers, denture irritation. Not for use in children under 12 years.	Adults, the elderly and children over 12 years: apply a small amount to the affected area with a clean fingertip. One application should be sufficient. It should not be used more frequently than every 3 hours.

Source: Electronic medicines compendium (EMC). Approved and regulated prescribing and patient information for licensed medicines. URL: https://www.medicines.org.uk/emc/ (accessed 16 August 2023).

20. Integrated benefit-risk statement

Lidocaine is a treatment option to relieve pain and discomfort from mouth ulcers/lesions in younger children and infants, and pain associated with medical procedures. There are approved products for these indications in New Zealand and in other countries.

The MARC highlighted that potential risks of toxicity of oromucosal lidocaine containing products in younger children and infants are dose related. Incorrect product use and accidental ingestion may lead to exposure of higher doses.

Since doses for children need to be calculated based on weight for some products and the indications for use of some products clearly requiring healthcare professional input, the classification should reflect these needs.

Healthcare professionals and consumers need to be aware of possible risks of toxicity with use of oromucosal lidocaine-containing products in younger children and infants, in particular, if accidental overdose or ingestion were to occur. Data sheets include information about these risks but are only mandated for Restricted and Prescription medicines.

21. Risk mitigating strategies

Caregivers and parents should be informed of potential risks related to excessive use of oromucosal lidocaine products and the importance of following the dosage recommendations for use in children.

Accidental ingestions of oral lidocaine products have been reported to NPC. Being OTC medicines, additional package information and/or advisory warnings may be needed to inform parents and caregivers to seek medical attention if more gel/solution is used than should be or if accidental ingestion were to occur.

Examples of possible risk minimisation measures to manage the potential risks of toxicity of oromucosal lidocaine products in younger children and infants include publication of a data sheet, changes to package labels and/or changes to classification.

Conclusion

The MARC recommended that oromucosal lidocaine products be referred to the MCC to review the classification of these products and consider whether mandatory label statements are needed on review of the risk of toxicity with use in younger children and infants.

Medsafe asks the MCC to consider in their review of classification: the indications for use, risk of side effects, potential for medication error, potential for overdose, and risk of accidental ingestion of oromucosal lidocaine products in children.

A preferred option of a restricted classification for use in children under 12 years of age is outlined noting the following:

Safety concerns: There have been overseas reports of serious adverse reactions in young children and infants when lidocaine 2% oral solution was used incorrectly or accidentally ingested. There have been reports to the New Zealand Poisons Centre of overdose requiring hospital review. The package labels do not provide sufficient warnings for a consumer to be informed of these risks. Healthcare professional input, such as pharmacist counselling is necessary to ensure the products are to be used appropriately, including safe storage.

Indications: Current indications for available products for use in children may not be appropriate for self-selection and diagnosis and in some cases alternative products should be considered first. Most products are also indicated for use related to pain prevention with procedures which would be performed by medical professionals.

Dose and administration: Current package labels either do not provide sufficient information about dose and administration or dosing is complex, requiring dose calculation. As a result, there may be increased risk of medication error when used by parents and caregivers. Pharmacist input will help parents and caregivers through counselling on how to use the product correctly.

Warnings: Restricted medicines are required to have a data sheet. There is limited information on the package label to include warnings about the importance of dosing and accurate administration. Having a data sheet can ensure that the pharmacist is aware of any possible risks and that these are relayed to the parents/caregiver.

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Appendix A

Table 10: Medicines Classification Committee history of consideration of lidocaine.

Medicines Classification Committee Meeting	Discussion and/ or Recommendations
MCC 1st Meeting (13.01.1984)	Recommended for *pharmacy-only:* except in medicines for external use containing 2% or less lignocaine.
MCC 7th Meeting (31.07-01.08.1990)	Recommended for: *Prescription*: in medicines for parenteral use and for internal use by ingestion other than throat lozenges. *Part II Pharmacy:* in medicines for external use containing more than 2% lignocaine. *General sales:* in medicines for external use containing 2% or less of lignocaine, and in throat lozenges.
MCC 8th Meeting (06.12.1991)	Recommended that 'lignocaine for eye use' should remain a *prescription* medicine but should have an exemption for optometrists should be made.
MCC 10th Meeting (11.11.1992)	Pharmacy Guild expressed concern that the 2% cut-off point for lignocaine has allowed a preparation presented in a urethral syringe to be sold as *general sales*. MCC concluded unlikely the company would market product through a supermarket or similar outlet. MCC expressed concern further restriction would limit sale of product by district nurses. MCC concluded no potential for harm with current classification.
MCC 11th Meeting (29.06.1993)	Clarification that a 2.5% lignocaine oral preparation would qualify as an external preparation. Explained definition of 'external use' in Medicines Regulations 1984.
MCC 13th Meeting (26.05.1994)	MCC received request the New Zealand Association of Optometrists had requested the addition of lignocaine and oxbuprocaine to the group of local anaesthetics exempt from prescription status when used in practice by registered optometrists. MCC agreed and recommendation was inline with proposal.

MCC 27th Meeting (23.05.2002)	Harmonisation of Aus and NZ Schedules consideration. Recommended: • That the *pharmacy-only* schedule entry for lignocaine be amended to impose an upper limit of 10% for external products and that the prescription entry be amended to accommodate the change. • That urethral use should be included as a *pharmacy-only* medicine. • That the NDPSC be asked to provide further information about the *pharmacy-only* classification of oral products containing up to 200 milligrams of lignocaine and details of products available in Australia.
MCC 55th Meeting (03.05.2016)	Medsafe noted that the use of term 'external use' in the *general sale* classification unintentionally excludes lignocaine throat sprays. MCC recommended that the general sales classification wording of lidocaine should be amended to: *General sales;* for external use and in throat sprays in medicines containing 2% or less; in throat lozenges in medicines containing 30 milligrams or less per dose form
MCC 58th Meeting (15.05.2017)	Recommended that: the classification statements of articaine, lignocaine and prilocaine with or without felypressin should be amended to include use by oral health therapists. A letter from the Dental Council, dated 16 May 2017, was tabled at the meeting after the committee had completed its deliberations. The letter confirmed information that was already included in the submission, that oral health therapists must hold and administer adrenaline for the management of an anaphylaxis event. The Committee made their recommendation before acknowledging this letter because it could be viewed as new information being presented at the meeting.
MCC 66th Meeting (11.05.2021)	Recommended: Lidocaine (Lignocaine): *Prescription;* except when containing 2.5% or less and used topically as a local anaesthetic in practice by a dental therapist or oral health therapist registered with the Dental Council.

MCC 69th Meeting (25.10.2022)	Recommended: Lidocaine (lignocaine): *Prescription* for injection except when used as a local anaesthetic in practice by a nurse whose scope of practice permits the performance of general nursing functions or by a podiatrist registered with the Podiatry Board or by a dental therapist, oral health therapist or dental hygienist registered with the Dental Council; except when containing 2.5% or less and used topically as a local anaesthetic in practice by a dental therapist, oral health therapist or dental hygienist (without local anaesthetic exclusion on their scope of practice) registered with the Dental Council; for ophthalmic use except when used in practice by an optometrist registered with the Optometrists and Dispensing Opticians Board; for oral use except in throat lozenges in medicines containing 30 milligrams or less per dose form; for external use in medicines containing more than 10%; except in throat sprays in medicines containing 2% or less; except when specified elsewhere in this schedule

Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

Oral lidocaine products: risk minimisation measures for use in teething

MHRA UK Public Assessment Report

December 2018

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1. Introduction

The Medicines and Healthcare products Regulatory Agency (MHRA) is the government agency responsible for regulating medicines and medical devices in the UK. We continually review the safety of all medicines in the UK and inform healthcare professionals and the public of the latest updates. In our Public Assessment Reports, we discuss evidence-based assessments of safety issues for a particular drug or drug class, and changes made to the product information on the basis of this evidence which will help safeguard public health.

The following MHRA Public Assessment Report discusses new risk minimisation measures which are being put into place for lidocaine-containing products that are used for teething in children.

2. Background

The MHRA conducted a review to assess the benefits and risks of oral lidocaine-containing products for treatment of teething. The review took into account available evidence from the wider literature, clinical guidelines, reports of side effects/adverse events available to the MHRA, National Poisons Information Service (NPIS) data, and information obtained from other European Union (EU) National Competent Authorities (NCA) and Marketing Authorisation Holders (MAH).

The MHRA review was passed to the Commission on Human Medicines (CHM; an independent body who gives advice to UK government Ministers about the safety, quality, and efficacy of medicines) for advice.

3. Teething in children

While symptoms associated with teething can be distressing for both the child and parent/carer, it must be remembered that this is a natural and self-limiting process.

The proposed mechanisms of tooth eruption "*include root elongation, hydrostatic pressure, periodontal ligament traction, bone remodelling and genetic pre-programming / cellular-molecular determinants*", according to Yeung & Chu (2014).

It is generally accepted that the constellation of symptoms associated with teething are not well understood (Yeung & Chu, 2014; Wise & King, 2008). Sometimes genuine underlying medical conditions such as gingivostomatitis may be present and falsely attributed to teething, while at other times symptoms may be harmless and unrelated to pain, therefore not amenable to treatment with oral anaesthetics. It may be extremely difficult for parents and carers to tell the difference.

As of December 2018, the National Institute for Health and Care Excellence Clinical Knowledge Summary (NICE CKS) on "Teething" recommendations for treating teething pain are to:

- Use a teething ring chilled in the refrigerator (not frozen) or another clean, cool object.
- Gently rub or massage the gums with a clean finger.
- Consider paracetamol or ibuprofen for relief of persistent symptoms in infants 3 months and older.

The advice document also states that "*topical anaesthetics and complementary therapies (such as herbal teething powder) are not recommended. Explain [to parents and carers] that there is no good evidence to support their use. However, if parents decide to use these treatments, advise them to follow the manufacturers' dosage recommendations. Severe adverse effects have been reported following inappropriate use of topical anaesthetics*."

4. Evidence

The reviews of the available efficacy and safety evidence for the use of oral lidocaine products for teething are summarised below:

Efficacy (how well it works)
A total of five clinical studies were considered in the review. These studies had design faults, which may have limited their ability to detect differences between treatment and control groups.

Three studies were identified to involve 2% oral lidocaine gels. One study demonstrated a statistically significant difference in pain intensity reduction at 3 minutes after treatment with 2% lidocaine gingival paste compared with placebo, in a very heterogeneous study population with a variety of "buccal wounds" (Co-ordination Group for Mutual Recognition and Decentralised procedures – Human, 2013). A second, small, exploratory study with 2% lidocaine gingival paste demonstrated a trend in parent-reported efficacy in teething infants but did not generate sufficient data for statistical analysis (Co-ordination Group for Mutual Recognition and Decentralised procedures – Human, 2013). Finally, Wolf & Otto (2015) demonstrated a statistically significant difference in pain intensity reduction at 10 ± 5 minutes and 30 ± 10 minutes after treatment with 2% lidocaine gingival paste when compared with placebo in the age group 4-8 years; however, this included a very heterogeneous study population with a wide range of oral conditions.

It should be noted that the efficacy results from studies of 2% lidocaine oral gel products are not directly translatable to lower concentration formulations currently licensed for use in children in the UK.

A fourth study; a double-blind trial compared 0.3% lidocaine/0.3% benzyl alcohol with placebo in 291 infants aged 5–31 months with teething pain (Seward et al., 1969). This trial is very old and has significant study design limitations, including an undocumented method to randomise patients to treatments (needed to minimise bias); a subjective, parent-rated efficacy endpoint, and uncontrolled application technique, which make it impossible to draw robust conclusions from the data.

A fifth study; a randomised, blinded trial compared 2% lidocaine with placebo, to determine if it improved oral fluid intake in 100 children aged 6 months to 8 years with ulcerative mouth conditions (Hopper et al., 2014). This too has significant study design limitations, including heterogeneous trial arms, significant placebo effect, and a non-validated surrogate marker of efficacy, which make it impossible to draw robust conclusions.

In summary, all the published studies were small and are difficult to interpret, mainly because they involved heterogeneous or incompletely described study populations (with conditions not limited to teething), heterogeneous or incompletely described medicinal products and dosing regimens, and non-validated subjective endpoints. There are no robust data providing convincing evidence of efficacy for oral lidocaine products in the treatment of teething in children.

Safety

Up to November 2017, a total of 197 paediatric adverse events reported via EU countries and MAHs, relating to oral lidocaine products and involving patients younger than 18 years old were identified.

The majority of all the adverse events were reported in babies younger than 1 years of age, although reports were present for all ages of children. There were 44 reports of accidental exposure to the product and 20 reports of known or suspected overdose in children. Most reports did not include an associated adverse event and were not thought to result in harm. Serious but rare adverse events included seizures, Stevens-Johnson syndrome, anaphylaxis and two deaths due to overdose reported in non-UK, literature articles but causality could not be established in all cases and other factors may have been associated.[1]

In addition, a total of 447 NPIS enquiries for accidental exposure or therapeutic error in patients less than 18 years old were made between 1st March 2013 and 26th September 2016, of which the majority (437) documented the poisoning severity as "none" or "minor", with the remainder (10) "unknown" or "not stated". Approximately a quarter (116) of NPIS enquiries related to children less than 1 year old.

An extensive review of safety information in the wider literature was also undertaken. One paper was identified that investigated the safety of oral lidocaine gels in children in general. Curtis et al. (2009) reviewed case reports from PubMed and data from the American Association of Poison Control Centres (AAPCC) between 1983 and 2003. The authors identified case reports involving patients aged 5–22 months of age. There was a case report of death of a boy, associated with significant elevated plasma lidocaine levels (19.5µg/ml, toxic) suggestive of overdose; a non-UK, literature case which was also identified in the MHRA pharmacovigilance database. Three seizures in children following topical lidocaine ingestion were also reported (all recovered), one of which caused respiratory arrest.

Other case reports identified in the wider literature include seizures in a 1-year old girl (Hess & Walson, 1988) and 11 month-old boy (Mofenson et al., 1983) treated with oral lidocaine products, a fatal accidental overdose in an 18 month-old child (Nisse et al., 2002) and an Australian case series (Balit et al., 2006) where similarities between paracetamol and lidocaine gel packaging led to 28 dosing errors in children, leading to two reports of adverse events (vomiting and increased salivation with solid dysphagia). Balit et al., 2006 also conducted their own literature search, and cited six further case reports of seizures related to oral lidocaine products in patients ranging from 5 months to 3 years of age (all recovered).

The concentrations of marketed oral lidocaine gels vary, and currently marketed formulations may not be the same as those described in the literature.

Exposure to the affected products is difficult to capture accurately, but MAHs estimate that more than 6 million packs of oral lidocaine products are sold per year in the UK. It is noted that there is a low rate of adverse event reports relative to the extensive use of these products. However, the number of accidental exposure, therapeutic error and overdose events among reports, NPIS enquiries, and the wider literature demonstrates that these products could be difficult to use correctly, without adequate advice, putting patients at risk of potential harm.

[1] Reports may be submitted if only a suspicion that the medicine may have caused the adverse drug reaction. The existence of an adverse drug reaction report does not necessarily mean that the medicine has caused the reaction.

Discussion of efficacy and safety data

Oral lidocaine teething products were authorised before current, more rigorous standards for demonstration of safety and efficacy of paediatric medicines. Although many of these products have been licensed and marketed for a long time, high-quality clinical data supporting their efficacy in teething are not available. All published trials have been small and are difficult to interpret. The concentrations of marketed oral lidocaine products vary, and currently marketed formulations may not be the same as those described in the literature, particularly in older reports, making it difficult to relate the limited available results to the indication and products currently under review.

In the review of the benefits and risks of these products, CHM identified a number of reports of medication error. Most reports did not include an associated adverse event and were not thought to result in harm, but the committee recommended that the administration instructions should be improved and harmonised to ensure parents and caregivers received consistent advice on the safe use of these medicines in babies.

CHM recommended that pharmacists were best placed to provide guidance to parents and caregivers on options for teething symptoms, including when symptoms could suggest more serious conditions that need medical assessment.

5. Expert advice

The Commission on Human Medicines (CHM) - the Government's independent expert advisors – advised the following new risk minimisation measures for the affected lidocaine products:

- Change of legal status of newly manufactured stock of oral lidocaine-containing products from general sale (GSL) to pharmacy (P).
- Update and harmonisation of posology and safety warnings across all oral lidocaine products authorised for teething.
- Restriction of the pack size of oral lidocaine products authorised for teething to a maximum of 10 grams.
- Re-positioning of oral lidocaine products as second-line, after non-pharmacological approaches.
- Update to oral, over-the-counter, lidocaine products licensed in children for other indications, and oral lidocaine products licensed in adults, to carry a warning against use in teething.

6. MHRA action

In December 2018, the MHRA announced the comprehensive package of measures set out in the advice from the CHM. The Drug Safety Update article is available on the MHRA website:
https://www.gov.uk/drug-safety-update/oral-lidocaine-containing-products-for-infant-teething-only-to-be-available-under-the-supervision-of-a-pharmacist

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Glossary:

General Sales List medicine
Medicines that can be bought from any shop without a prescription

Labelling
Information on the immediate or outer packaging of a medicine

Lidocaine
A drug that causes a numbing action when applied to body surfaces (a local anaesthetic)

Marketing authorisation holder
The company or other legal entity that has the authorisation to market a medicine in the UK

National competent authority
A medicines regulatory authority in a European Union Member State

Pharmacy medicine
Medicines that can only be sold to a customer by a trained pharmacist

Risk minimisation measure
A public health intervention intended to prevent or reduce the probability of the occurrence of an adverse reaction associated with exposure to a medicine or to reduce its severity if it occurs.

Contacts to the New Zealand National Poisons Centre regarding exposures to specific products with lidocaine in 2018-2023

Date of report: **15 August 2023**

Methods and aims

Time frame investigated: 1 January 2018 to 30 June 2023 (5.5 years)

Extraction criteria: Contacts to the National Poisons Centre (NPC), and all records relating to human patients **aged 0-3 years** exposed to lidocaine-containing liquid/gel-formulation medicines that are dosed topically onto the oral mucosa.

Key words used in extraction: lidocaine, lignocaine, Xylocaine (Viscous), Mucosoothe, Medijel

Significant data limitations to be noted

1. Contacting the NPC is voluntary, and the exposures that are reported only describe a subset of all similar exposures occurring in Aotearoa New Zealand. There is no information available that can determine what proportion of all exposures NPC hears about.

2. Exposures are documented as reported by the caller, and there is no independent confirmation of the identity of the substances involved. E.g., if someone phones NPC concerned about Xylocaine exposure, that is how it is documented in NPC records. The person may have been mistaken about the identity of the product or substance. NPC advises on the next steps in assessment and treatment after an exposure based on available information and an individual case risk assessment.

3. Importantly, NPC records report "exposures" with a subset resulting in "poisonings." The term "poisoning" implies the development of a harmful physiological effect after exposure to a substance. Exposure-related calls make up the majority of the NPC call volume. The NPC may recommend medical evaluation to observe for the development of harmful effects based on defined risk criteria, even if no effects are present at the time of the contact. NPC does not collect comprehensive outcome data about exposures. Reaching intervention criteria does not automatically denote harm to the patient. Medical referral advice may be a better proxy for exposure-related risk rather than actual harm; a medical referral does not always imply that harm has actually occurred (or will occur).

Summary of identified exposures

A total of 9 human exposure records were identified, and all were ingestions. The circumstances of these exposures are presented in Table 1. Four patients ingested at least half a tube of a product, and four patients reached the intervention level (referral for medical assessment) of 6 mg/kg lidocaine ingested. All patients were asymptomatic at the time of the contact with NPC. There are too few cases to comment on trends over time in the number of exposures.

Table 1: Exposures to specific lidocaine products in human patients.

Patient age in years	Year	Reason	Product	Amount ingested	Dose mg/kg
0	2018	Therapeutic error	Xylocaine 2% 'teething gel'	~1g of gel	3.1
3	2019	Therapeutic error	Mucosoothe Oral Gel 2%	~3ml of gel	3.3
0	2020	Child exploratory	Medijel	Half a tube (7.5g)	4.4
3	2020	Child exploratory	Xylocaine 2%	"Small amount"	Below INCR
2	2020	Child exploratory	Lignocaine 2% gel	~5g of gel	**6.7****
1	2020	Child exploratory	Lignocaine 2% gel	~2.5ml of gel	4.2
1	2023*	Child exploratory	Medijel	~14g (almost a whole tube)	**8.1****
3	2023*	Child exploratory	Medijel	~13g (almost a whole tube)	**6.1****
1	2023*	Child exploratory	Medijel	15g (whole tube)	**7.6****

INCR = intervention criteria; a limit where a patient will likely be sent in for medical assessment. This includes reaching an ingested dose of 6 mg/kg in the case of ingestions of lidocaine. *January-June included in search for cases. **Above INCR.

Comment

Reports to NPC regarding lidocaine oral gel exposures in children aged 0-3 years involved unintentional exposures such as therapeutic errors and child exploratory ingestions whereby a child gained unsupervised access to a container of the product.

Further information

For any questions related to this document please contact NPC director Dr Adam Pomerleau at adam@poisons.co.nz.