Medicines Adverse Reactions Committee

Meeting date	14/09/2023	Agenda item	3.2.1
Title	**Oral lidocaine-containing products and risks of toxicity in younger children and infants**		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice

Active ingredient	**Product name**	**Sponsor**
Lidocaine	Xylocaine Jelly	Pharmacy Retailing (NZ) Ltd t/a Healthcare Logistics
Lidocaine	Xylocaine Pump spray	Pharmacy Retailing (NZ) Ltd t/a Healthcare Logistics
Lidocaine hydrochloride	Xylocaine Viscous	Pharmacy Retailing (NZ) Ltd t/a Healthcare Logistics
Lidocaine hydrochloride	Mucosoothe	Orion Laboratories (NZ) Ltd
Lidocaine hydrochloride	Lidocaine Gel 2%	Orion Laboratories (NZ) Ltd
Lidocaine hydrochloride and Aminoacridine hydrochloride	Medijel Gel	Wilson Foods Limited

PHARMAC funding	Mucosoothe (Community Schedule) Lidocaine Gel 2%, Mucosoothe, Xylocaine Pump spray (Hospital Schedule)
Previous MARC meetings	This topic has not previously been discussed at a MARC meeting.
International action	• Food and Drug Administration (US) Drug Safety Communication: FDA recommends not using lidocaine to treat infant teething pain and requires new box warning (2014). • Health Canada (Canada) Safety Review: Viscous lidocaine 2% - assessing the potential risk of severe side effects in infants and young children (2016). • Medicines and Healthcare products Regulatory Authority (UK) Drug Safety Update: Oral lidocaine-containing products for infant teething: only to be available under the supervision of a pharmacist (2019). • Therapeutic Goods Administration (Australia) Safety Review: Proposed changes to Required Advisory Statements for Medicine Labels (RASML): Lidocaine (2021)
Prescriber Update	Medsafe have previously communicated about adverse reactions resulting from the improper use of topical anaesthetics, including lidocaine. • Adverse reactions to topical anaesthetics *Prescriber Update* 30 (2): 10 May 2009
Classification	Lidocaine when used for external use in medicines containing: • 2% lidocaine or less is a general sale medicine • 10% lidocaine or less and more than 2% lidocaine is a pharmacy only medicine • more than 10% is a prescription medicine

Usage data	See section 2.1.4.
Advice sought	**The Committee is asked to advise:** • Is there a potential for oral lidocaine-containing products to cause toxicity in younger children and infants in New Zealand? • If yes, does this apply to all oral lidocaine-containing products irrespective of strengths? • Is regulatory action required to reduce potential risks of harm that affected products may pose within this age group (noting that different risk minimisations measures may be required depending on the product (i.e., Xylocaine Pump Spray, Xylocaine Viscous, Mucosoothe, Lidocaine Gel 2%, Xylocaine Jelly, Medijel Gel))? • Is further communication needed for this topic, other than MARC's Remarks?

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1 PURPOSE

Previous international regulatory authority safety communications have highlighted reports of serious adverse reactions with use of oral mucosal (applied to mucous surfaces of the mouth) lidocaine-containing products in younger children and infants [1,2,3].

In New Zealand, oral lidocaine-containing products are available over the counter for topical anaesthesia of the mouth and may be used for treatment in younger children and infants.

This paper outlines the information available for oral lidocaine-containing products and risks of toxicity in younger children and infants.

2 BACKGROUND

2.1 Lidocaine

2.1.1 Pharmacology

Lidocaine (lignocaine) is a local anaesthetic and provides loss of sensation (numbing) to an area of the body. It is also a type 1b antiarrhythmic agent [4].

Lidocaine blocks voltage-gated sodium channels, which prevents sodium influx, subsequent depolarization, and action potential generation. This conduction block impedes the pain transmission from neuronal cells to the cerebral cortex, thereby producing anaesthesia and analgesia [4].

2.1.2 Classification

Table 1 outlines conditions when lidocaine is a prescription, pharmacy only and general sale medicine in NZ.

When administered via the oral mucosal route, lidocaine-containing products that contain up to 10% are classified as non-prescription medicines. Depending on the strength of lidocaine, the product may be sold as a pharmacy only or general sale medicine.

Table 1: Classification of lidocaine in New Zealand, as per Classification Database

Classification	Conditions
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: Medsafe. Classification Database. 17 May 2019. URL: https://www.medsafe.govt.nz/profs/class/classintro.asp (accessed 16 August 2023)

Comments: Depending on the conditions for use, lidocaine may be a prescription, pharmacy only or general sale medicine.

'External use' includes lidocaine containing medicines that are applied via the oral mucosal route such as viscous solution or gels.

There are currently no restrictions within the classification data base relating to the indication or age groups of use for oral lidocaine-containing products when sold as pharmacy or general sale medicines.

2.1.3 Indications

Lidocaine is used in many different clinical situations for its anaesthetic properties to relieve pain or to prevent pain related to a procedure [4, 5].

Various routes of administration of lidocaine are available including injection, creams, gels, sprays, and viscous solution. The choice is dependent on the intended use and affected area [4].

The strength of lidocaine products varies depending on product type and administration route [4].

Comments: Lidocaine is widely used for many indications.

This paper will focus on approved lidocaine containing products that provide topical anaesthesia in the mouth and may be used for treatment of younger children and infants.

2.1.3.1 Topical anaesthesia of oral mucosa

Lidocaine may be used for relief of pain from conditions within the oral mucosa or for prevention of pain related to procedures, such as within dentistry or introduction of instruments to the gastrointestinal tract [5].

Inflammation of the oral mucosa

Mucosal diseases of the oral cavity are relatively common, and there are a number of types that may occur in children. Commonly encountered mucosal lesions are those of an epithelial break (mucosal ulcer) or an alternation in thickness, texture, or colour (white, red, or pigmented lesion) [6,7].

An ulcerated lesion is most commonly traumatic (for example from biting) or immunological (aphthous) in origin. Other causes include an oral malignancy, infective (bacterial or fungal) or immune-related causes (e.g., inflammatory bowel disease). Persistent ulcers that have been present for more than two weeks should be further investigated for the underlying cause [6,7].

Gingivostomatitis is an inflammation of the oral mucosa and gingiva (gums). It is the most common manifestation of primary herpes simplex virus (HSV) infection during childhood. It causes ulcerative lesions of the gingiva and mucous membranes of the mouth, often with perioral vesicular lesions [8].

Oral mucositis is an inflammation of the oral mucosa, usually following systemic cancer therapy and/or radiation therapy. Lesions are often very painful and may impact oral intake [9].

The diagnosis of mouth conditions is clinical, and if symptomatic, treatment primarily involves pain relief and the provision of sufficient oral fluid intake to prevent dehydration. Lidocaine viscous solutions or oral gels may be a treatment option to provide relief of pain and discomfort of irritated or inflamed oral mucosal membranes [6,7].

Oral viscous lidocaine solutions are designed to be 'swished' around the mouth and then spat out, or applied to the affected area by a cotton swab. Care must be taken after use, and administration of food in the first 60 minutes after administration is not recommended. Accidental biting of the oral mucosa may occur as a result of anaesthetic effects [5].

Efficacy

Whilst lidocaine viscous may be widely used for symptomatic mouth pain in adults and children, there are limited controlled trials to evaluate efficacy [8,10].

Hopper et al (2014) assessed whether 2% viscous lidocaine is better than placebo at increasing oral intake in children with infectious mouth conditions aged 6 months to 8 years of age. The study did not find evidence that viscous lidocaine improved oral intake during the first hour after administration compared to placebo. There were limitations to the study, particularly, the use of fluid intake as a primary measure, which may have many confounding factors. It was suggested that methylcellulose, which was a component in both the 2% viscous lidocaine and placebo, may have provided a coating effect on the ulcers, increasing oral intake [11].

Coudert et al (2014) assessed the efficacy in pain reduction of 2% lidocaine cream compared to a placebo in children aged 6 – 15 years with oral mucosal lesions or for use in dental procedures. The results of the study showed efficacy for a single dose of 2% lidocaine cream versus placebo for symptomatic relief of pain due to lesions in the oral cavity or from dental procedures within this age group. The reporting of pain by younger children may not be an accurate measure of treatment efficacy, due to variables in perception of pain [12].

Wolf & Otto (2015) analysed the efficacy and safety of a 2% lidocaine gel in children from 6 months up to 8 years with painful conditions in the oral cavity. Treatment was applied once, by or under supervision of a member of study staff to the painful affected area as a pea size amount (0.2g) corresponding to 4mg lidocaine hydrochloride. The primary efficacy variable was the pain reduction measured from the participant or their parent or caregiver. The study showed that 2% lidocaine gel was statistically significantly better at reducing pain versus placebo in children aged over four years of age. Children under the age of four only received 2% lidocaine gel, and not placebo. 40.6% of these children reported improvement of pain [13].

Comments: Lidocaine may be a treatment option to relieve pain and discomfort relating to mouth ulcers/lesions in younger children and infants.

There are limited available randomised controlled trials which assess the efficacy and safety of lidocaine applied to the oral mucosa in children. In addition, there are conflicting results. Limitations to these studies include age of participants, pain perception measured by children or their parents/caregivers, and single doses administered.

Hopper et (2014) conducted their study in Australian emergency departments (ED). While the study included children aged six months to eight years, the average age of participants was around two years of age. This may highlight that younger child with mouth ulcers/lesions may be more likely to present to ED within Australia, than older children. The study also highlighted how 2% lidocaine viscous was used in Australia ED departments as a treatment in younger children and infants with mouth ulcers/lesions during at the time.

Infant teething

Eruption of primary teeth (teething) is an expected, natural part of child development and is associated with minor self-limited signs and symptoms [14,15].

Infant teething usually begins between age six and 10 months. The emergence of the tooth through the gum generally takes place over an eight-day period comprising four days prior, the day of eruption and then four days of final eruption. All primary teeth have usually erupted by age 30 months [14, 15].

Teething may cause discomfort from painful, swollen gums, as the teeth break through. Symptoms of teething may include excessive drooling, chewing/mouthing, appetite loss and generally unsettled behaviour. Sometimes systemic symptoms are reported, however there is no evidence that the symptoms are caused by teething [14,15].

Management of teething is symptomatic and includes self-care measures, and oral analgesia such as paracetamol or ibuprofen if required. Self-care measures include gently rubbing the gum with a clean finger and allowing the infant to bite on a clean cool object, such as a teething ring [14].

Infant teething gels containing lidocaine are also available. Some guidelines do not recommend use of lidocaine for infant teething due to lack of evidence and potential for harm [14, 16].

The National Institute for Health and Care Excellence Clinical Knowledge Summary on teething treatment recommends using non-pharmacological measures such as a teething ring chilled in the refrigerator or to gently rub/massage the gums. Topical anaesthesia and complementary therapies are not recommended. Parents and caregivers should be informed that there is no good evidence to support their use. If parents decide to use these treatments, the manufacturers dosage recommendations should be strictly followed [3].

Use of topical anaesthetics for teething is discouraged by the American Academy of Paediatrics. Non-pharmacological methods are recommended [4].

Procedures

Lidocaine may be used to numb specific areas of the body before minor surgery, dental or other procedures to reduce pain and discomfort [5,17,18].

Topical lidocaine mucosal preparations have been shown to decrease the pain of intraoral dental injections. [19].

Comments: Lidocaine may be used to provide pain relief for oral mucosal lesions or prior to pain provoking procedures.

Lidocaine may also be used in infant teething; however, its use is not recommended in some guidelines.

2.1.3.2 Approved oral mucosal lidocaine-containing products in New Zealand

Table 2 outlines oral mucosal lidocaine-containing products that may be used in younger children and infants, approved in NZ, by indication and classification.

Xylocaine Pump spray, containing lidocaine 10%, is approved for use to prevent pain associated with introduction of instruments, tubes, and catheters into the respiratory and digestive tract [18]. It is a pharmacy only medicine and is also funded by PHARMAC for use in hospital only [20]. A published data sheet is available [18].

Mucosoothe oral topical gel is a generic version of Xylocaine Viscous oral solution and is currently funded by PHARMAC for use in the community and hospital [20]. Both products contain lidocaine 2% and are pharmacy only medicines that may be used in younger children and infants for the relief of pain and discomfort of mucous membranes of the mouth, throat, and upper gastrointestinal tract. Xylocaine Viscous is also indicated for the introduction of instruments and catheters into the respiratory and gastrointestinal tract. Use of either product is not recommended in teething pain as per label warnings. A published data sheet is available for Xylocaine Viscous [5].

Medijel Gel contains lidocaine hydrochloride 0.66% and aminacrine hydrochloride 0.05% (antibacterial). It may be used for the relief of pain from infant teething, mouth ulcers, sore gums, and denture-rubbing [21].

Lidocaine 2% Gel is approved for topical anaesthesia and anaesthesia of mucous membranes where lubrication is required [22]. Xylocaine Jelly is also a topical gel that can be applied to mucous membranes, mostly with regards to procedures [17].

Table 2: Approved lidocaine-containing products for oral mucosal use, by dose form, strength, indication and classification

Product name (Approval date)	Dose form	Lidocaine strength	Indication	Classification[c]
Xylocaine Pump Spray[a] (1969)	Oral spray	10%	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: Provides surface anaesthesia for the oropharyngeal and tracheal areas to reduce reflex activity, attenuate haemodynamic responses and facilitate insertion of the tube or the passage of instruments during endotracheal intubation and endoscopic procedures of the airways and upper gastrointestinal tract. Dental practice: Before injections, dental impressions, X-ray photography, removal of calculus.	Pharmacy only
Xylocaine Viscous[a] (1997)	Oral solution	2%	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. Indicated for the relief of pain and discomfort associated with introduction of instruments and catheters into the respiratory and gastrointestinal tract	
Mucosoothe[b] (2016)	Oral topical gel	2%	Indicated for the relief of pain and discomfort of mucous membranes of the mouth, throat, and upper gastrointestinal tract.	
Xylocaine Jelly[a] (1969)	Topical gel	2%	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.	
Lignocaine Gel 2%[b] (1987)	Topical gel	2%	For topical anaesthesia and anaesthesia of mucous membranes where lubrication is required.	General sale
Medijel Gel[b] (1988)	Topical gel	0.66%	Relief of pain from infant teething, mouth ulcers, sore gums and denture-rubbing.	

Source: a) Medsafe. Data sheet and consumer medicine information. 24 May 2020. URL: https://www.medsafe.govt.nz/Medicines/infoSearch.asp (accessed 15 August 2023) b) Medsafe. Evaluation filing, product labelling. (accessed 15 August 2023) c) Medsafe. Product/Application Search. 3 September 2021. URL: https://www.medsafe.govt.nz/regulatory/DbSearch.asp (accessed 16 August 2023)

Comments: On review of oral lidocaine containing products available in NZ, there are a range of non-prescription products that may be administered to the oral mucosa in younger children and infants.

Xylocaine Pump spray contains 10% lidocaine and is approved only for pain relating to procedures.

Medijel Gel is the only product which is specifically labelled for use in infant teething. It is also labelled to use for mouth ulcers, sore gums and denture irritation. Parents or caregivers are able to self-select this medicine and use for these indications in younger children and infants over the age of 6 months.

Mucosoothe and Xylocaine Viscous are pharmacy only medicines. Mucosoothe is funded on prescription.

Lidocaine 2% Gel and Xylocaine Jelly are topical gels that may be applied to mucous membranes, including the oral mucosa. Xylocaine Jelly has more specific indications for use compared to Lidocaine 2% Gel.

Further information of these six products is outlined in section 3.1.1.

Other oral lidocaine-containing products are available, however, are not included in this paper as are either not recommended for use in children under six years of age, or for use in adults only. Examples include lower strength lidocaine sprays and lozenges for sore throats and a prescription periodontal gel.

2.1.4 Usage

2.1.4.1 Medijel Gel

2.1.4.2 Lidocaine oral (gel) solution 2%

Table 4 outlines the number of dispensings for lidocaine oral (gel) 2% i.e., Xylocaine Viscous oral solution or Mucosoothe topical oral gel as per the Pharmaceutical Data web tool.

Table 4: Number of dispensings of lidocaine oral (gel) 2%

Year	Number of dispensings[a]	Number of people[b]
2019	8,661	6,878
2020	8,269	6,309
2021	8,915	6,835

a) Number of times the pharmaceutical product is dispensed from a pharmacy to the named person on all occasions including repeats (except for administrative dispensings such as owed balances) during the year.
b) Number of people who received a dispensing of the pharmaceutical product as a named person from a pharmacy at least once during the year (includes people who only received a repeat dispensing during the year.

Source: Te Whatu Ora, Pharmaceutical Data web tool version 7 November 2022 (data extracted from the Pharmaceutical Collection on 10 August 2022). URL: https://tewhatuora.shinyapps.io/pharmaceutical-data-web-tool/ (accessed 16 August 2023).

2.1.4.3 Lidocaine gel 2% tube

Table 5 outlines the number of dispensings for lidocaine 2% gel/jelly i.e Xylocaine Jelly or Lidocaine Gel 2% per the Pharmaceutical Data web tool.

Table 5: Number of dispensings of lidocaine oral (gel) 2%

Year	Number of dispensings[a]	Number of people[b]
2019	686	386
2020	917	541
2021	1210	741

a) Number of times the pharmaceutical product is dispensed from a pharmacy to the named person on all occasions including repeats (except for administrative dispensings such as owed balances) during the year.
b) Number of people who received a dispensing of the pharmaceutical product as a named person from a pharmacy at least once during the year (includes people who only received a repeat dispensing during the year.

Source: Te Whatu Ora, Pharmaceutical Data web tool version 7 November 2022 (data extracted from the Pharmaceutical Collection on 10 August 2022). URL: https://tewhatuora.shinyapps.io/pharmaceutical-data-web-tool/ (accessed 16 August 2023).

Comments: As per the Pharmaceutical Data web tool, there have been more dispensing from community pharmacies of lidocaine oral gel/solution, compared to lidocaine gel/jelly.

A limitation of the Pharmaceutical Data web tool is that it only includes dispensing information from community pharmacies. Usage may be higher incorporating OTC sales and hospital use.

While these products are approved for use in children, it is not known how many of the dispensings are for younger children and infants. Therefore, the use of these products in this age group is not known.

2.1.5 Risks of toxicity in younger children and infants

Comments: This paper will focus on the risks of severe adverse reactions highlighted from previous regulatory drug safety communications relating to lidocaine toxicity with use of lidocaine viscous in younger children and infants.

It is acknowledged that there may be other adverse reactions related to lidocaine and other anaesthetics such as methemoglobinemia, however these are not reviewed in this paper.

2.1.5.1 Local anaesthetic systemic toxicity

Local anaesthetic systemic toxicity (LAST) is a life-threatening adverse reaction that may occur at high plasma concentrations of local anaesthetics, including lidocaine. Primarily the central nervous systems and cardiovascular systems are affected [23].

Toxicity generally occurs as a result of therapeutic error and may occur after any route of administration of local anaesthetics. Situations leading to toxicity include inadvertent venous or arterial injection, as well as excess doses of ingested or topically administered local anaesthetic-containing preparations [23, 24].

Increasing plasma concentrations of local anaesthetics initially compromises inhibitory pathways by blockage of sodium voltage gated channels, disrupting inhibitory neuron membrane depolarisation. Inhibiting these pathways leads to excitatory clinical features. As the plasma concentrations of local anaesthetic rise, excitatory pathways are affected, producing a depressive phase of neurological toxicity. Within the cardiovascular system, normal conduction is disrupted by sodium channel blockage [25].

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). Cardiovascular symptoms may occur along with or after CNS symptoms, and may include hypertension or hypotension, tachycardia, or bradycardia, followed by ventricular arrhythmias. Effects on the cardiovascular system may be more likely seen in severe cases, typically after signs of CNS toxicity. Cardiac arrest may occur as a result of high systemic concentrations, with potentially fatal outcome [23].

The presentation and speed of progression of symptoms depend on the route of systemic absorption, local anaesthetic plasma level, how quickly the concentration rises (rate of absorption), and the characteristics of the specific local anaesthetic. If signs of toxicity occur, treatment should be stopped immediately, and symptoms promptly treated [23].

LAST is dose dependent and the risk is higher at elevated plasma concentrations. Therefore, the most critical aspect of local anaesthetics therapy is appropriate dosing and administration. Signs of serious lidocaine toxicity may occur at plasma concentrations greater than 6 microgram/mL [25,26].

Many factors may influence plasma levels in addition to use of higher doses, including repeated administration and reduced elimination (such as in renal or hepatic impairment). Infants and young children and the elderly may also be more susceptible to toxicity [23].

2.1.5.2 Risks in oral mucosal administration of lidocaine

Systemic absorption

When lidocaine-containing products such as gels or solutions are administered to the oral mucosa, lidocaine may be systemically absorbed via mucous membranes or via the gastrointestinal tract if swallowed [27,28].

When lidocaine is applied to the oral mucosa, the onset of action occurs with 3 – 5 minutes. 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 [5,17,28].

If lidocaine is swallowed, it undergoes extensive first pass hepatic metabolism before being systemically absorbed. The bioavailable of ingested lidocaine is about 35%. Lidocaine that has been swallowed reaches peak concentrations in approximately 40 minutes [28].

Risks for toxicity

Seizures have been reported in association with intake of lidocaine viscous 2% in paediatric patients. A review by the FDA highlighted reports of toxicity, including seizures, severe brain injury and cardiovascular problems, with lidocaine viscous 2% solution in children aged 5 months to 3.5 years. The majority of the reports noted administrative errors, using higher doses than prescribed, and accidental ingestion [1].

It is recommended that if lidocaine viscous 2% solution is used in children, the lowest effective dose is administered. The dose should not exceed 4 mg/kg/dose (0.2 mL/kg). Doses may need to be individually adjusted according to the patients age, weight, and physical condition [19].

The risk of toxicity in younger children and infants with lidocaine oral gels/solutions may be impacted by difficulties in administration of these products in this age group. Dosing of Lidocaine viscous is weight based. Measuring devices for measuring the correct volume to ensure accuracy of dose are recommended. The dose can be applied using a cotton swab to the affected area, especially if unable to 'swish and spit' [4,15].

The risk of ingestion of oral 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 removed from the affected area. To reduce risks related to excess use, dosing instructions should be strictly adhered to [4,15].

If oral lidocaine-containing products have been accidently ingested or large doses administered, the dose of ingestion should be calculated in mg/kg. 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 [24].

Comments: Lidocaine is a local anaesthetic with a narrow therapeutic index, that may cause dose-dependent toxicity. Younger children and infants are likely more susceptible.

Reports of toxicity, including seizures, have occurred in young children and infants with lidocaine viscous 2% solution. The reactions were often related to medication error, excessive or prolonged use or accidental ingestion. The risk of toxicity with lower strength lidocaine solutions/gels may be less clear.

Doses over 6mg/kg ingested by children require hospital assessment.

3 SCIENTIFIC INFORMATION

3.1 Product information

Product information of oral lidocaine-containing products that may be used in younger children and infants from NZ and other countries were reviewed.

3.1.1 New Zealand

1. Xylocaine Pump spray

Xylocaine Pump spray may be used in children aged between 3 – 12 years of age. In children less than 3 years of age, section 4.2 of the data sheet states that less concentrated lidocaine solutions are recommended [18].

A maximum dose of 3 mg/kg is recommended in children aged 3 – 12 years of age. When used mainly in the larynx and trachea the dose should be reduced to 1.5 mg/kg [18].

A published data sheet for Xylocaine Pump spray is available. There are currently no specific warnings in relation to risks of toxicity when used in younger children. In section 4.4 and 4.8, there is general information relating to excessive dosage and acute toxicity [18].

The package labelling for Xylocaine Pump spray is highlighted in figure 1.

Figure 1 (a): Xylocaine Pump Spray, package label (bottle)

Figure 1 (b): Xylocaine Pump Spray, package label (outer carton)

Comments: While Xylocaine Pump spray is a pharmacy only medicine, it is likely that when used for its approved indications it is administered in hospital under the guidance of healthcare professionals. The package label includes a warning 'For professional use only'.

The data sheet includes risks relating to high plasma levels and serious adverse effects, however, does not include younger children may be more susceptible.

2. Xylocaine Viscous and Mucosoothe

Xylocaine Viscous and Mucosoothe may be used in younger children and infants for topical anaesthesia of the mouth, and upper gastrointestinal tract [5,29].

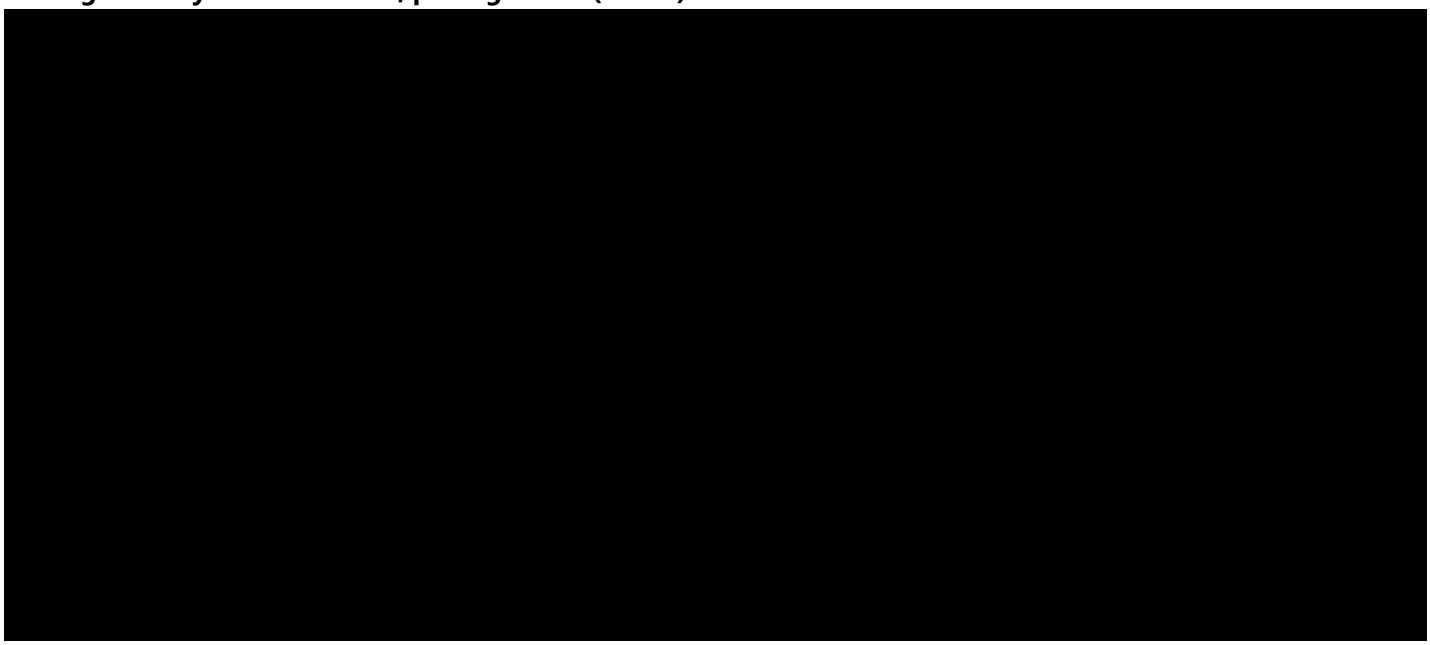
Figure 2 outlines the package label for Mucosoothe, which includes information about how the product should be administered. Lower doses are recommended for children compared to adults, including less frequent application. In children less than three years of age, Mucosoothe should be accurately measured and applied only to the affected area with a cotton swab. In children aged 3 - 12 years, the solution should be spat out if using for anaesthesia of the mouth [29].

Warnings included on the package label note that the product it not to be used for teething pain, and not to eat within 60 minutes of use [29].

Figure 2: Mucosoothe, package label (bottle)

Figure 3 outlines the package label for Xylocaine Viscous. Different to Mucosoothe, the Xylocaine Viscous package label does not include a maximum of four doses in 24 hours for children.

Figure 3: Xylocaine Viscous, package label (bottle)



A published data sheet is available for Xylocaine Viscous and provides additional information to the package label about risks of use in paediatric patients (table 6) [5].

Section 4.4 of the data sheet includes a warning relating to use in paediatric patients. This warning includes 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. 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. To decrease the risk of serious adverse events with use of Xylocaine Viscous, it is recommended to instruct caregivers to strictly adhere to prescribed dose and frequency of administration and store the bottle in a safe way out of reach of children [5].

Table 6: Xylocaine Viscous oral solution data sheet, information on toxicity and use in children

Section	Information (*note only information included if related to toxicity and/or use in children, see data sheet for full prescribing information)
4.2	At the present time there is not enough documentation to allow recommendations for a more prolonged use of Xylocaine Viscous in children under the age of 3 years. The solution should not be administered to sooth teething pain in infants and children because of safety concerns.
4.4	Warning: Excessive dosage, or short intervals between doses, can result in high levels of lignocaine or its metabolites and serious adverse effects. In order to prevent serious adverse effects, patients should be instructed to strictly adhere to the recommended dosage and administration guidelines. The management of serious adverse reactions may require the use of resuscitative equipment, oxygen and other resuscitative drugs. Patients should not exceed the recommended dose or use Xylocaine Viscous for prolonged periods except on the advice of their physician. The lowest dose that results in effective anaesthesia should be used to avoid high plasma levels and serious adverse effects. Tolerance to elevated blood levels varies with the status of the patient. Following too high or repeated doses, including accidental ingestion of viscous lignocaine in infants and children under the age of three years, serious side effects have been reported involving the cardiovascular and central nervous systems including fatal outcomes. Patients should be instructed to adhere strictly to the recommended dosage. This is especially important in children where the doses vary with weight.
4.4	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. Xylocaine viscous should not be administered to infants and children for teething pain. For other conditions, the 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. To decrease the risk of serious adverse events with use of xylocaine viscous, instruct caregivers to strictly adhere to the prescribed dose and frequency of administration and store the bottle safely out of reach of children.
4.4	Absorption from wound surfaces and mucous membranes is relatively high, especially in the bronchial tree. Because of the possibility of significant systemic absorption, Xylocaine Viscous should be used with caution in patients with traumatised mucosa and/or sepsis in the region of the proposed application. In order to prevent serious adverse effects, if the dose or site of administration is likely to result in high blood levels, lignocaine, in common with other local anaesthetics, should be used with caution in patients with epilepsy, impaired cardiac conduction, bradycardia, impaired hepatic function, in severe shock, the elderly, patients in poor general health and patients with severe renal dysfunction.
4.8	Systemic adverse reactions are rare and may result from high plasma levels caused by excessive dosage or rapid absorption, or may result from a hypersensitivity, idiosyncrasy or reduced tolerance on the part of the patient. Such reactions are systemic in nature and involve the central nervous system and/or the cardiovascular system. Central Nervous System - CNS reactions are excitatory and/or depressant and may be characterised by lightheadedness, nervousness, apprehension, euphoria, confusion, dizziness, drowsiness, tinnitus, blurred vision, vomiting, sensations of heat, cold or numbness, twitching, tremors, convulsions, unconsciousness and possibly respiratory arrest. The excitatory reactions may be brief or may not occur at all, in which case the first manifestations of toxicity may be drowsiness, progressing to unconsciousness and respiratory arrest. Drowsiness following administration of lignocaine is usually an early sign of a high blood level of the drug and may occur as a result of rapid absorption. Cardiovascular - Cardiovascular reactions are usually depressant and may be characterised by hypotension, myocardial depression, bradycardia and possibly cardiac arrest

Source: Pharmacy Retailing (NZ) Limited t/a Healthcare Logistics. 2019. Xylocaine Viscous solution New Zealand data sheet. 2 May 2019. URL: https://www.medsafe.govt.nz/profs/Datasheet/x/xylocaineviscoussol.pdf (accessed 16 August 2023).

Comments: In relation to potential risks of toxicity with use of Xylocaine Viscous or Mucosoothe in younger children and infants, the following is noted on review of Xylocaine Viscous data sheet and package labelling of both Xylocaine Viscous and Mucosoothe:

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.

As the dose is weight based, there may be possibility of higher doses used in children who may be overweight.

Duration of use

There are currently no warnings on 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 three years.

Frequency of use

The Xylocaine Viscous package label does not include a maximum of four doses in 24 hours in children, while this information is in the data sheet and on the Mucosoothe package label.

No lower age limit for use

No lower age for use in children is noted on the package labelling for both products, nor in the Xylocaine Viscous data sheet.

Indications for use

Section 4.4 of the Xylocaine Viscous data sheet includes that use of the product in patients less than three years of age should be limited to those situations where safer alternatives are not available or have been tried but failed due to post-marketing reports of seizures, cardiopulmonary arrest, and death when not administrated in strict adherence to dosing and administration recommendations.

This information would be preferable also in section 4.2, to notify healthcare professionals that this product is not recommended as first line treatment in this age group due to safety concerns.

There is no such warning on the package label of Mucosoothe or Xylocaine Viscous. 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.

Warnings

While not required to have a data sheet as it is a pharmacy only medicine, the Xylocaine Viscous data sheet contains important information in relation to the use of the product in children under the age of three. In section 4.4 information is included relating to risks of toxicity in younger children and infants, and the importance of following dosing and administration recommendations. This information is important for awareness relation to the potential for toxicity for healthcare professionals and providing education to parents and caregivers.

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.

At present, there is only a published data sheet for Xylocaine Viscous, and not for Mucosoothe.

Other

As a consideration for accidental ingestion by younger children, Mucosoothe and Xylocaine Viscous are 200 mL bottles (20mg/mL = 4,000mg lidocaine). These products have a child resistant cap.

3. Medijel Gel

Medijel Gel may be used for the relief of pain from infant teething, mouth ulcers, sore gums, and denture-rubbing. It is currently the only product containing lidocaine available for use in infant teething in NZ [21].

Figure 4 outlines the package labelling, which includes the directions, administration instructions, and warnings for use.

Figure 4 (a): Medijel Gel, package label (outer carton)

Figure 4 (b): Medijel Gel, package label(tube)

Medijel Gel may be used in children from the age of 6 months. Administration instructions for Medijel Gel are the same regardless of the indication. The instructions include that application may be repeated after 20 minutes if necessary [21].

The Medijel Gel product label includes to avoid excess and prolonged treatment for infant teething disorders [21].

Comments: Medijel Gel is currently the only product available containing lidocaine that is indicated for infant teething.

It is classified as a general sale medicine, however, is labelled as a pharmacy only medicine. This is being further reviewed by Product Regulation team within Medsafe for label compliance.

Potential concerns for risk of toxicity when used in younger children and infants are noted below:

Dose and administration

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

Warnings

There are currently no warnings on the package label relating to possible risks of harm from overdose or excessive use in younger children or infants. There is no package leaflet or data sheet.

The risk of toxicity with Medijel may be less likely due to a lower concentration of lidocaine (0.66%) versus in lidocaine viscous (2%). Therefore, risk minimisation measures may not be as relevant for this product.

Use in infant teething

The use of lidocaine in infant teething is not recommended by some guidelines (NICE guidelines and American Academy of Paediatrics recommendations). 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).

Other

Medijel also contains alcohol as an excipient (10%).

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

4. Lidocaine Gel 2% and Xylocaine 2% Jelly

Comments: This paper focuses on use of Lidocaine Gel 2% and Xylocaine Jelly on the oral mucosa.

It is acknowledged that they may be used at other mucosal sites, however these are not discussed.

Lidocaine Gel 2% is a pharmacy only medicine that may be used by children 12 years and under for topical anaesthesia and anaesthesia of mucous membranes where lubrication is needed [22].

Figure 5 outlines the outer carton product label for Lidocaine Gel 2%, which includes warnings and directions for use.

Figure 5 (a): Lidocaine Gel 2%, package label (outer carton)

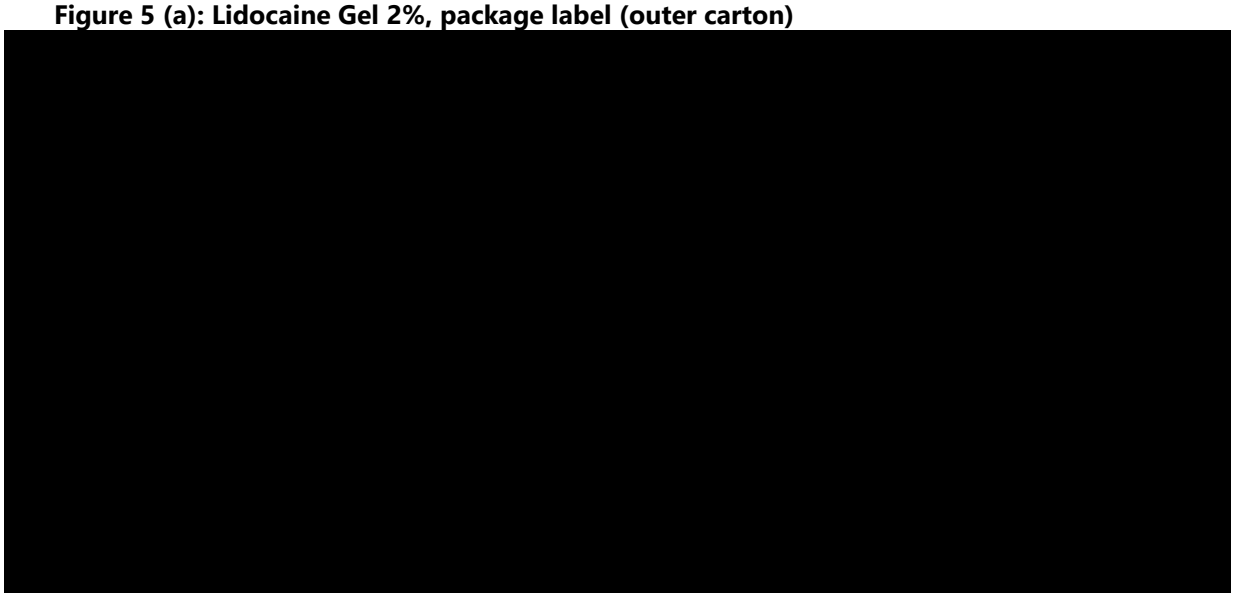


Figure 5 (b): Lidocaine Gel 2%, package label (tube)

Lidocaine Gel 2% may be applied to any part of the body. Warnings included in the package label include that absorption from mucous membranes is relatively high and that excess gel should be removed. The product is not recommended for use in infant teething. Use is only recommended on medical advice [22].

Xylocaine Jelly 2% is approved for use as a surface anaesthetic and lubricant for procedures, such as cystoscopy, gastroscopy, and bronchoscopy. Similar to Lidocaine Gel 2%, the dose in children up to 12 years of age is up to 6mg/Kg [17].

Figure 6 outlines the package label for Xylocaine Jelly.

Figure 6 (a): Xylocaine Jelly, package label (outer carton)

Figure 6 (b): Xylocaine Jelly, package label (outer carton)

Figure 6 (c): Xylocaine Jelly, package label (tube)

A data sheet is available for Xylocaine Jelly 2%, which includes additional information relating to directions for use and administration. It is recommended that no more than four doses should be given in a 24-hour period. The data sheet includes some information similar to Xylocaine Viscous data sheet relating to excessive doses and serious adverse effects, however a warning for paediatric use is not included [17].

Comments: Potential concerns for risk of toxicity for use in younger children and infants within the oral mucosa are noted below:

Application site

Indications for use for these products are 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 via this route.

If used within the oral mucosa, these products may be more likely be used to prevent pain with pain provoking procedures, rather than treatment of pain relating to ulcers or other oral lesions. As a result, it may be more likely that a healthcare professional will be involved in administration of the product, and that use would be for a one-off occasion. They may also be used within dentistry.

There are specific indications such as endoscopy listed for adults and children over 12 years of age. No further information is provided for children under 12 years of age.

A data sheet for Xylocaine Jelly is available and provides further information for dosing and administration compared to the package label.

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.

Age of use

There is no lower age of use.

Warnings

The package labels include a warning relating to high absorption from mucous membranes. The package label for Lidocaine Gel 2% includes that that the product should not be used for infant teething.

The Xylocaine Jelly 2% data sheet does not include information about potential risks relating to paediatric patients or about use in infant teething.

The risks related to use of Lidocaine Gel 2% and Xylocaine Jelly on the oral mucosa in younger children and infants may be lower due to the indications for use of these medicines. However, it may be possible that the products could be used for other indications where topical anaesthesia of the oral mucosa is required.

Toxicity is possible if excessive doses are given, however, whether these products are routinely used within the oral mucosa is not known, as the indications for use are quite broad.

Other

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

Summary (NZ)

The risk of potential excessive and/or prolonged use, medication error or accidental ingestion of oral lidocaine-containing products in younger children and infants may vary with different products, noting the current information on package labels and/or data sheets, the differences in strengths of lidocaine and the indications and possible settings for use.

Some product information may not be adequate and may require additional risk minimisation measures for safety.

As with any medicine product when sold as a pharmacy only or general sale medicine, consumers rely on the package label as the primary source of information. A healthcare professional is not required as part of the sale. There are currently no warning and advisory statements that are required for lidocaine-containing products as per the Label Statements Database.

3.1.2 United Kingdom

In the UK, some lidocaine-containing gels or solutions available OTC may be used for temporary relief of pain caused by recurrent mouth ulcers, denture irritation, and for infant teething. Table 7 highlights further information about these products [3].

Table 7: 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[a]	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[b]	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 ect +/- infant teething			
Anbesol liquid	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.	Babies teething and children: apply to the affected area 0 25mL of undiluted liquid by covering the bottle mouth with a clean finger tip, 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	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	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	Lidocaine hydrochloride 2%, chlorocresol 0.1%, cetylpyridinium chloride 0.02%	For the temporary relief of pain caused by recurrent mouth ulcers, denture irritation.	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).

Lidocaine-containing products for infant teething, mouth ulcers and denture irritation contain less than 2% in the UK. Products that are used only for infant teething contain 1% or less [3, 30].

Following the MHRA review in 2018, harmonised directions for use for lidocaine products used for infant teething were introduced as risk minimisation measures. Instructions for use in teething include to use a 'pea sized' amount, to not use more frequently that every three hours, and use no more than six doses in 24 hours. The use of teething gels is also recommended only when non-pharmacological treatments have failed to provide sufficient relief [3].

The classification of lidocaine teething gels was changed to pharmacy only as a risk ministration measure to ensure that the products are used appropriately [3].

There are additional warnings within the summary of product characteristics (SmPC) for lidocaine gels used in infant teething in the UK that may aid in limiting excessive use. In section 4.2 of the SmPC, it is recommended that treatment should be stopped once symptoms have resolved. In addition, the product should not be used for more than 7 days. Parents or carers should seek medical attention if the child's condition deteriorates during treatment. In case of vomiting, spitting or accidental ingestion, the dose should not be repeated immediately. Another application may be administered after three hours if required [30].

Lidocaine products also contain patient information leaflets (PIL) which provide further information to parents and caregivers how to use the product, in addition to the package label. Similar information to the SmPC is included. In addition, the PIL includes that if the gel is used more than it should be or if large quantities of the gel are accidently swallowed, to contact a doctor or go to the nearest emergency department, even if the child seems well [30].

Lidocaine products that are not indicated for infant teething are required to include a warning to not use in infant teething because they have different approved dosing regimens [3].

Higher strength oral lidocaine products, such as Anbesol Adults strength gel contains 2% lidocaine, and is indicated for adults and children over the age of 12 years [30].

Comments: Lidocaine-containing products are available in the UK for relief of pain associated with teething, mouth ulcers, and denture irritations.

In comparison to Medijel Gel (NZ), lidocaine teething gels in the UK have more restrictions on use.

While the MHRA review noted the lack of efficacy for use of lidocaine in teething, products are available for this indication from a pharmacy, under the supervision of a pharmacist. All products have similar dose instructions (independent of lidocaine strength), including amount per application, dose frequency and maximum daily dose. In addition, products are restricted to second line increasing the chance that the product is only used when clearly needed. These measures were implemented to reduce risks of potential medication error or excessive use.

The MHRA review specifically looked at the use of lidocaine for infant teething, however there are lidocaine gels/solutions available in the UK, for treatment of mouth ulcers in infants from 5 months of age, that contain less than 1% lidocaine. This poses the questions as to whether the risks relating to overdose, excessive or prolonged use for lower strength products, are related to the indication or to the medicine itself. Lower strength lidocaine solutions/gels may be less likely to cause toxicity, such as when use of higher doses is restricted through appropriate use and administration and dosing instructions.

Mouth ulcers may be less common in younger children and infants compared to infant teething and may be less likely to cause symptoms. Teething may also occur over longer periods of time, which may promote prolonged use. In addition, application of gel to teething, may be over a wider area, when compared to an ulcer, therefore increasing risks relating to systemic absorption.

3.1.3 Australia

Mucosoothe and Xylocaine Viscous are available in Australia as pharmacy only medicines. The products have similar labelling, indications, dosing, and warnings to NZ data sheet [31, 32].

Following a consultation undertaken by the TGA in 2021, products containing more than 1.5% lidocaine are required to have a warnings statement 'do not use for infant teething pain' [33].

SM-33 Gel is a pharmacy only oral mucosal gel for the temporary pain-relieving treatment of mouth ulcers, new dentures, abrasions and inflammation of the gums, palate, and tongue. The product contains lidocaine 0.5%, in addition to salicylic acid 0.25%, sodium salicylate 2.03%, tannic acid 0.5%, menthol 0.05%, thymol 0.05%, glycerol 20% and ethanol 40%. Directions for use are to apply to the affected area every 3 hours [34].

Xylocaine 2% Jelly is also a pharmacy only medicine, that has similar indications, dosing, and administration instructions to the NZ product [35].

Comments: There are no lidocaine containing products approved for infant teething in Australia, however lidocaine gel is available for use in younger children and infants for other indications.

The Australian Xylocaine Viscous oral solution product information is the same as the NZ data sheet, noting post market reports of seizures from use of the product in children less than three years of age.

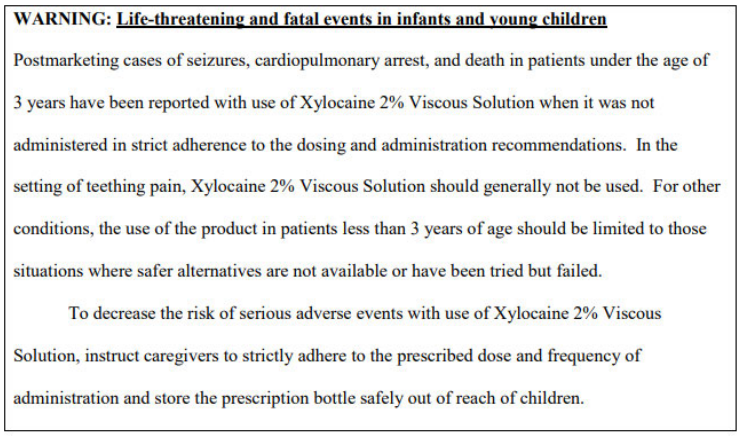
Some lidocaine products sold OTC in Australia are required to have warnings labels to not use in infant teething. It is noted that these required statements have also been introduced on the same products marketed in NZ following harmonisation with Australian package labelling.

3.1.4 USA

Lidocaine Viscous solution is a prescription medicine approved by the FDA. It is indicated to produce topical anaesthesia of irritated or inflamed mucous membranes in the mouth and pharynx. It is also useful to reduce gagging during X-rays and when creating dental impressions. It is not licensed for use in infant teething [36].

Lidocaine Viscous product labels are required to have a 'black box' warning following the FDA review of safety reports related to lidocaine viscous solution use in younger children and infants. Figure 4 outlines the black box warning in the Xylocaine 2% Viscous solution product label [1,36].

Figure 4: Xylocaine 2% Viscous black box warning



WARNING: Life-threatening and fatal events in infants and young children

Postmarketing cases of seizures, cardiopulmonary arrest, and death in patients under the age of 3 years have been reported with use of Xylocaine 2% Viscous Solution when it was not administered in strict adherence to the dosing and administration recommendations. In the setting of teething pain, Xylocaine 2% Viscous Solution should generally not be used. For other conditions, the 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.

To decrease the risk of serious adverse events with use of Xylocaine 2% Viscous Solution, instruct caregivers to strictly adhere to the prescribed dose and frequency of administration and store the prescription bottle safely out of reach of children.

Source: Fresenius Kabi. 2014. Xylocaine 2% Viscous Solution FDA Label. September 2014. URL: https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/009470s025lbl.pdf (accessed 18 August 2023).

The FDA label includes under precautions that parents/caregivers should be cautioned about the following [36]:

- For patients under three years of age, special care must be given to accurately measuring the prescribed dose and not administering the product more often than prescribed.
- To ensure accuracy, we recommend you use a measuring device to carefully measure the correct volume.
- The product should only be used for the prescribed indication.
- To reduce the risk of accidental ingestion, the product container should be tightly closed, and the product should be stored well out of reach of all children immediately after each use.
- If the patient shows signs of systemic toxicity (e.g., lethargy, shallow breathing, seizure activity) emergency medical attention should be sought immediately, and no additional product should be administered.
- Unused product should be discarded in a manner that prevents possible exposure to children and pets.

Comments: Lidocaine viscous 2% is a prescription medicine in the US.

As discussed above, the Xylocaine Viscous data sheet includes a warning noting post market reports of serious adverse reactions. The wording of this warning is noted to be similar to the FDA black box warning.

The FDA label includes information for patients relating to risks of toxicity and preventative measures.

3.1.5 Canada

Xylocaine Viscous and Xylocaine Jelly are marketed in Canada. The product monographs for these products include that lidocaine should be used in caution in children younger than two years of age as there is insufficient data to support the safety and efficacy in this population group at this time [37,38}.

Xylocaine Jelly 2% has similar indications to those in the Xylocaine Jelly NZ data sheet. In children aged 2 – 11 years, the maximum amount of Xylocaine Jelly 2% should not exceed 6 mg/kg per dose or 3 mL per 10 kg body weight. No more than four doses should be given during a 24-hour period [38].

Table 8 outlines information in Xylocaine Viscous and Xylocaine Jelly product monographs relating to risks of toxicity in younger children and infants.

Table 8: Health Canada Xylocaine Product Monographs, information on risks of toxicity in younger children and adults

Product label	Information
Use in children	Lidocaine should be used with caution in children younger than two years of age as there are insufficient data to support the safety and efficacy of this product in this patient population at this time.
Post market reports in children (Xylocaine Viscous)	*Life-threatening and fatal events in infants and young children* 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 2% solution due to accidental ingestion, or accidental overdose when it was not administered in strict adherence to the dosing and administration recommendations.
Use in paediatric patients (Xylocaine Viscous)	XYLOCAINE Viscous 2% should not be administered to infants and children for teething pain. XYLOCAINE Viscous 2% should be used with caution in children under the age of 2 as there is insufficient data to support the safety and efficacy of this product in this patient population at this time. Use in this patient population should be limited to those situations where safer alternatives are not available or have been tried but failed. To decrease the risk of serious adverse events with use of Xylocaine Viscous 2% solution, instruct caregivers to strictly adhere to the prescribed dose and frequency of administration and store the prescription bottle safely out of reach of children. Children should be given reduced doses commensurate with their age, weight and physical condition because they may be more sensitive to systemic effects due to increased blood levels of lidocaine. Care must be taken to ensure correct dosage in all paediatric patients as there have been cases of overdose due to inappropriate dosing. The solution should not be swallowed. Children should swish or gargle the solution, then spit it out. For young children with difficulty spitting out the solution, the dose and solution must be accurately measured and applied to the affected area only, with a cotton tip applicator.
Use in children (Xylocaine Jelly)	When using XYLOCAINE Jelly 2% in younger children, especially infants under the age of 3 months, care must be taken to ensure that the caregiver understands the need to limit the dose and area of application and to prevent accidental ingestion Children should be closely observed during and after use of topical anaesthetics, as they are at greater risk than adults for serious adverse events

Source:

- Aspen Pharmacare Canada Inc. 2018. Xylocaine Viscous 2% product monograph. 12 July 2018. URL: https://pdf.hres.ca/dpd_pm/00054987.PDF (accessed 18 August 2023).
- Aspen Pharmacare Canada Inc. 2020. Xylocaine Jelly 2% product monograph. 10 September 2020. URL: https://pdf.hres.ca/dpd_pm/00058090.PDF (accessed 18 August 2023).

3.1.6 European Union

Anbesol Anaesthetic Antiseptic oral mucosal solution contains 0.9% lidocaine hydrochloride (in addition with chlorocresol and cetylpyridiniun chloride) and is a non-prescription medicine marketed in Ireland [39].

The product is indicated for the symptomatic relief of mouth ulcers and sore gums. It not recommended in children under 10 years of age [39].

An SmPC is available, which outlines important information relating to toxicity in section 4.9 [39]:

- Serious toxicity is usually due to inadvertent intravenous overdosage. It is much less likely after oral administration because of extensive first pass metabolism but has been reported after ingestion of large amounts.
- Lidocaine is readily absorbed across mucous membranes and through damaged skin.
- Systemic toxicity and death have been reported in children and adults following ingestion or aspiration of topical solutions or viscous preparations. The effect may also be due to absorption of high concentrations across the buccal mucosa causing systemic toxicity.
- Signs of serious toxicity may occur at plasma concentrations greater than 5-8 microgram/mL (5-8mg/L).
- All patients who have taken a deliberate overdose should be referred for assessment.
- Children and adults who have ingested 6mg/kg or more lidocaine, or those who are symptomatic, should be referred for medical assessment.
- Children and adults who have accidentally ingested less than 6mg/kg lidocaine and who have no new symptoms since the time of ingestion do not need to be referred for medical assessment. Patients should be advised to seek medical attention if symptoms develop.

Dynexan mouth gel is marketed in Germany and contains 2% lidocaine. The product is indicated for mouth ulcers and infant teething. As per the company website, the product is approved for use with no age restriction. The recommended dose 4mg of lidocaine up to four times a day. This equals approximately 16mg per day or 2.2 mg/kg in a 7.3Kg average weight six-month year-old child [40, 41].

Comments: There are OTC lidocaine containing products available in Europe. Not all counties include infant teething as an approved indication.

The Ireland SmPC for Anbesol Anaesthetic Antiseptic oral mucosal solution contains important information relating to toxicity and oral ingestion.

3.1.7 Summary (international)

Oral lidocaine-containing products are available in several countries for topical anaesthesia within the oral mucosa and may be used in younger children and infants.

Classification

In the US, Lidocaine viscous is a prescription medicine, whereas in Canada it is a pharmacist medicine.

Similar to NZ, lidocaine viscous 2% is a pharmacy only medicine is Australia.

Lidocaine teething gels in the UK are available from a pharmacy only.

Indication

Lignocaine containing gels for infant teething are approved in NZ, Germany, and UK.

Products in the UK have more details for directions and warnings for use compared to NZ.

OTC oral lidocaine-containing products are available for other indications in younger children and infants overseas, in addition to NZ.

Similar to NZ, use of Xylocaine Viscous in Canada in younger children should be limited to those situations where safer alternatives are not available or have been tried but failed.

Age

Health Canada product monographs include that 'lidocaine should be used with caution in children younger than two years of age as there are insufficient data to support the safety and efficacy of this product in this patient population at this time'.

Dose

In the UK, directions for use of teething gels include the amount to give, the frequency of application and maximum daily dose. A maximum duration of treatment is also provided.

Administration

The FDA and Health Canada product information for lidocaine viscous include additional information relating to patient education, and the importance of correct dosage and administration.

Warnings

Information in black box warnings in the FDA label are included in the Xylocaine Viscous oral solution NZ data sheet.

Package leaflets of UK lidocaine OTC products contain information about if the product is used more than it should be or if accidental ingestion occurs.

An Ireland SmPC includes information in section 4.9 relating to accidental ingestion, and doses that require medical assessment.

3.2 Literature

A literature search focussed on toxicity of oral lidocaine containing lidocaine products in younger children and infants which resulted in mostly identification of case reports with lidocaine viscous 2%.

3.2.1 Are teething gels safe or even necessary for our children? A review of the safety, efficacy and use of topical lignocaine gels – Teoh & Moses, 2020 [15]

This is an opinion article summarising the evidence for efficacy and safety of lidocaine when used in teething gels.

Accurate dosing of teething gels is difficult to achieve, and overenthusiastic application can result in toxicity. Application of the gel in the oval cavity makes it hard to determine the actual dose administered to the child as it quickly becomes mixed with saliva which increases the risk of swallowing and ingestion. This risk is further increased if the child is crying, drooling, or salivating more due to teething. Swallowing also anaesthetises the child's mucous membrane, increasing the risk of aspiration.

The authors comment on the UK MHRA review (section 4.1.3), and states that there is 'no robust data providing convincing evidence of efficacy for oral lidocaine products in the treatment of infant teething'.

The authors also review literature case reports, of which some are further discussed below and the FDA drug safety communication (section 4.1.1).

In light of the lack of high-quality clinical data to support the efficacy of topical lignocaine gel in teething and the high number of global case reports documenting severe adverse reactions to topical lidocaine gel when used in young children and infants, the authors question the benefit and safety of lidocaine gels in this indication.

Orally applied lignocaine products were originally marketed prior to the modern practice of evidence-based medicine at a time when they were generally considered safe.

Teething is an expected, physiological process associated with self-limited discomfort. There is a documented risk of toxicity with lignocaine gel and. global dental organisations do not recommended use of topical agents

for teething., Therefore, the authors call on regulatory authorities such as the Therapeutic Goods Administration to consider a change of indication and/or scheduling for these products.

All health care workers, including those directly working with parents and care givers such as lactation consultants and midwives should also be informed of the risks of this medicine to ensure that all care givers receive consistent advice.

Comments: This opinion article highlights how lidocaine containing products were originally marketed prior to evidence-based medicine.

Some lidocaine products were approved a long time ago.

In 2021, the TGA took regulatory action in relation to lidocaine and infant teething, following FDA and Health Canada's safety reviews.

3.2.2 Lignocaine and chlorhexidine toxicity in children resulting from mouth paint ingestion: A bottling problem – Balit et al, 2006 [42]

These authors report a case series of lidocaine and chlorhexidine mouth paint ingestion (containing lidocaine 20 mg/mL and chlorhexidine 0.5 mg/mL) in a paediatric population.

This product was marketed in Australia by the Women's and Children's Hospital in Adelaide for the relief of 'infant teething'. The packaging of the product was very similar to that of a paediatric paracetamol preparation, and in some cases, the incorrect product was administered.

Cases were identified from the New South Wales Poisons Information Centre and the Western Australian Poison Information Centre, in Australia, between June 2001 to July 2003. Cases where the exact dose of ingestion was unknown were excluded.

28 cases were identified with complete follow up. The median age was 11 months (range 2 months – 4 years). The mean ingested dose of lidocaine was 2.7 mg/kg (standard deviation 1.2), and the largest ingested dose was 5.9 mg/kg. The mean ingested dose of chlorhexidine was 0.06 mg/kg (standard deviation 0.03), and the largest dose was 0.15 mg/kg.

Two children developed adverse effects. One child was distressed and unsettled, with increased salivation. The other vomited twice within 30 minutes of ingestion. No reports of seizures or arrythmias were identified.

Discussion

The authors reviewed the literature for reports of lidocaine and chlorhexidine ingestion in children. A summary of the reports for lidocaine exposure is outlined in table 9 below.

Table 9: Summary of previously reported cases of oral lidocaine exposure, dosage, and clinical effects

[redacted]

The authors conclude that doses of lidocaine ingestion under 6 mg/kg are highly unlikely to cause significant symptoms. Doses more than 6 mg/kg are likely to cause symptoms that may require observation.

Severe toxicity is unlikely unless doses more than 15 mg/kg are ingested. All previous case reports of severe effects following lidocaine ingestion in children were in the range 25 – 50 mg/kg with only one case of 14 mg/kg.

Clinical effects would be expected to occur within the first one-two hours following ingestion.

Comments: This article reviewed case reports or accidental ingestion of lidocaine containing teething mouth paint. The mean ingested dose of lidocaine was 2.7 mg/kg. No seizures or arrythmias were identified.

On review of the literature, the authors concluded that doses more than 6 mg/Kg are likely to cause symptoms that may require observation.

3.2.3 Fatal intoxication of twin girls after ingestion of topical 2% lidocaine viscous – Nefy et al, 2017 [43]

The authors outline a fatal case report.

Case

Twin 13-month-old girls were treated with 2% lidocaine viscous for teething pain by their paediatrician. Both presented separately but within 48 hours of each other with generalised tonic-clonic seizures, followed by cardiac arrest.

Serum testing revealed toxic concentrations of lidocaine.

It appeared that the infants had been administered the medicine in their milk bottles because of incessant crying, and that the solution had been confused with paracetamol.

Discussion

While uncommon, systemic toxicity from orally ingested viscous lidocaine is potentially a devastating complication of overdose, especially in cases of poor caretaker health literacy.

Clinicians should be aware of the potential for intoxication and reserve topical anaesthetics for situations where they are absolutely necessary.

3.2.4 Seizures secondary to oral viscous lidocaine – Hess & Walson, 1988 [44]

The authors outline two case reports of children who developed central nervous system toxicity following oral administration of viscous lidocaine.

Case 1

A 1-year-old girl was prescribed 2% viscous lidocaine hydrochloride for gingivostomatitis. She experienced a depressed level of consciousness and generalised seizures, after being given 800 – 1000mg of 2% viscous lidocaine over a 9–12-hour period. A serum lidocaine level of 7.4 micrograms/mL was obtained approximately 70 to 90 minutes after the last dose of viscous lidocaine had been administrated.

She was treated with antiepileptics, and seizures stopped.

Case 2

A 5-month-old boy was given 100mg of 2% viscous lidocaine hydrochloride for teething. The medicine was not prescribed to the child. It belonged to another family member and was used without medical advice. Several hours after administration, the child had a seizure. Serum lidocaine levels drawn six and seven hours after the last dose were 3.9 micrograms/mL and 2.2 micrograms/mL.

Discussion

The improper use of viscous lidocaine may result in central nervous system toxicity in young children.

Clinicians must be aware of the potential risks and carefully review dosing schedules, potential toxicity with parents and also consider alternative options.

Prolonged administration, or overuse from frequent, repeated administration, may allow accumulation of toxic metabolites, and increase the risk of toxicity.

3.2.5 Lidocaine toxicity from topical mucosal application – Mofenson et al, 1982 [45]

This author describes a case of an infant who experienced seizures when treated with a topical lidocaine 2% solution (Xylocaine 2% Viscous)

Case

An 11-month-old male experienced a seizure and was admitted to hospital. The child had been prescribed lidocaine 2% solution for teething. The mother had been applying the solution to the infants gums with her finger five to 6 times daily for the past week.

Lidocaine serum level taken was 10 micrograms/mL, a toxic level associated with seizure activity.

Discussion

Serious adverse systemic reactions to lidocaine have been reported after ingestions of the topical dosage form.

In this case, it was difficult to determine whether the toxic lidocaine level was on the bases of the chronic application of lidocaine to the mucous membrane and the accumulation of lidocaine, or its metabolites, or the swallowing of a large amount acutely. Lidocaine intoxication by the gastrointestinal route following topical application was considered to the cause for the seizure.

When topical anaesthetics are applied to the oral mucosa, it would appear important to have the patient expectorate the excess to avoid absorption. Since children under seven years of age are unable to expectorate, unless taught to do soe, these agents pose a risk to them.

The authors note concern about the use of the medicine in infants and small children. There is lack of evidence and safety for lidocaine hydrochloride to be used for symptoms attributed to eruption of teeth.

3.2.6 Recurrent seizures after lidocaine ingestion – Aminiahidashti et al, 2016 [46]

The authors describe a case report of seizure after ingestion of 2% lidocaine hydrochloride in a 4-year-old boy.

Case

The boy presented to hospital due to a tonic-clonic generalized seizure. Approximately three hours before the seizure, he was mistakenly given 2 spoons of 2% lidocaine hydrochloride solution instead another medicine.

Neurological examination was unremarkable except for depressed level of consciousness. Personal and medical history were also unremarkable.

Serum lidocaine concentration 30 minutes after the onset of seizures was 5.1 microgram/mL.

Discussion

Oral ingestion of 5 – 25 mL of 2% viscous lidocaine has resulted in seizures in children.

Conservative management is the best option for treatment of lidocaine-induced seizure.

Comments: There are literature case reports where use of 2% lidocaine viscous led to seizures in young children. In these reports, frequent, prolonged and/or overuse contributed to toxicity. Some cases had fatal outcomes.

Symptoms of toxicity are likely to occur within hours of use, however, may occur due to repeated dosing.

The possibility of lidocaine toxicity from lower strengths (< 2%) is unclear, however may be theoretically possible following excessive ingestion or incorrect use.

Healthcare professionals should be aware of the potential for toxicity in younger children and infants if using lidocaine gel/solutions and consider alternative options.

Available products should appropriately manage risks through directions and warnings for use, and classification.

Randomised controlled trails that have reviewed the safety and efficacy of lidocaine oral solutions/gels in children, often used one dose, administered by a health professional. In this setting, adverse effects relating to toxicity would be less likely.

4 Regulatory action

4.1 Food and Drug Administration (FDA), United States of America

FDA drug safety communication: FDA recommends not using lidocaine to treat teething pain and requires new Boxed Warning [1]

In 2014, the US Food and Drug Administration (FDA) warned that prescription oral viscous lidocaine 2% solution should not be used to treat infants and children with teething pain.

The FDA reviewed 22 case reports of serious adverse reactions, including deaths, in infants and young children 5 months to 3.5 years of age who were given oral viscous lidocaine 2% solution. Fifteen cases were identified in FDA's Adverse Event Reporting System (FAERS) and seven additional cases were noted in the literature.

Of the 22 cases, 6 resulted in death, 3 were categorised as life threatening, 11 required hospitalisation and 2 required medical intervention without hospitalisation.

The root cause of the overdose in 7 of the 22 cases was the administration technique by the caregivers, who did not follow prescriber directions for application of the product or gave additional doses beyond what was prescribed. Accidental ingestion occurred in 7 additional cases, and four cases involved overdose due to prescribing error. The root cause of the error could not be identified in the remaining four cases.

The reported reasons for use of lidocaine in these 22 cases, where available, was teething pain (n=5), oral stomatitis (n=6), fever blister (n=1), thrush (n=2), oral ulcer/lesion (n=3), and sore throat due to croup (n=1).

Of the 22 cases, multiple doses of lidocaine taken prior to the onset of the adverse event occurred in 11 cases. In 6 cases, the toxicity manifested following the accidental ingestion of a single dose.

Healthcare professionals should not prescribe or recommend oral lidocaine 2% solution for teething pain. When too much viscous lidocaine is given to infants and young children or they accidently swallow too much, it can result in seizures, severe brain injury and cardiac problems. Cases of overdose due to wrong dose or accidental ingestion have resulted in infants and children being hospitalised or dying.

The FDA required a *Box Warning* to be added to the medicine label and updates to warning, dosage, and administration sections. The product is not approved by the FDA to treat teething pain. Other approved uses are under supervision of a healthcare professional.

Comments: Following the review of spontaneous reporting in the US, the FDA strengthened information in the label for 2% lidocaine viscous solution and included Black Box warning.

In addition, they recommended that lidocaine vicious 2% should not be used for infant teething.

4.2 Health Canada, Canada

Summary Safety Review (Viscous Lidocaine 2%) – Assessing the potential risk of severe side effects in infants and young children [2]

In 2016, Health Canada carried out a safety review to assess the potential risk of severe side effects in infants and young children with the use of viscous lidocaine. The issue was triggered by the FDA safety announcement that viscous lidocaine should not be used for teething pain in infants and children.

In Canada, 2% viscous lidocaine is used to reduce pain and discomfort in the mouth or to numb an area in the mouth before a medical exam or procedure in the mouth area. Products are available without a prescription from a pharmacist.

Following the review, although the product information includes that use is not recommend using viscous lidocaine 2% for teething pain, the product labelling and dosing for some products did not specify how much

time should be left between doses. This could lead to high levels of lidocaine, resulting in the severe side effects reported in infants and young children.

The review concluded that there is a link between 2% lidocaine viscous and severe side effects (seizures, severe brain injury, heart problems, and death) in infants from 5 months to 4 years of age. Health Canada worked with pharmaceutical companies of the affected products for labelling updates, and to clarify directions for approved uses.

Comments: Similar to the FDA, Health Canada have updated product labels with information about the risk of severe adverse reactions in younger children and infants with 2% lidocaine viscous solution.

4.3 Medicines & Healthcare products Regulatory Agency (MHRA), United Kingdom

Oral lidocaine products: risk minimisation measures for use in teething, MHRA UK Public Assessment Report [3]

In 2018, the MHRA reviewed the benefits and risks of oral lidocaine products for teething.

A summary of the Public Assessment Report, recommendations by the Commission on Human Medicines (CHM) and regulatory action taken by the MHRA is provided below.

Efficacy

A total of five clinical studies were considered in the review. Two of these are discussed in 2.1.3.1 (Hopper et al, Wolf & Otto), and another two in section 4.4.

The other study was a double-blind trial which compared 0.3% lidocaine/0.3% benzyl alcohol with placebo in 291 infants aged 5-31 months with teething pain. This trial was very old and had significant study limitations, including an undocumented method to randomise patients to treatment, a subjective, parent-related efficacy endpoint and uncontrolled application technique, which made it impossible to draw robust conclusions from the data.

In summary, all the published studies were small and difficult to interpret, mainly because they involved heterogenous or incompletely described study populations (with conditions not limited to infant teething), heterogeneous or incompletely describe 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 manufacturing authorisation holders 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 children of all ages. 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.

A total of 447 enquires for accidental exposure or therapeutic error in patients less than 18 years of age were made to the National Poisons Information Service (NPIS) between 1 March 2013 and 26 September 2016. The majority documented the poisoning severity as ‘none’ or ‘minor’. 116 enquires were related to children under 1 years of age.

On review of the wider literature, case reports were identified relating to topical lidocaine ingestion. Of note, the concentrations of marketed oral lidocaine gels vary, and currently marketed formulation may not be the same as those described in the literature.

Overall, there is a low rate of adverse reaction reports relative to the sales information for oral lidocaine products in the UK. However, the number of accidental exposure, therapeutic error and overdose among reports, NPIS enquires and the wider literature, demonstrate that these products could be used incorrectly, without adequate advice, putting patients at risk of potential harm.

Discussion

Oral lidocaine teething products were authorised before current, more rigorous standards for demonstration of safety and efficacy of paediatric medicines were developed. 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 errors. 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.

Recommendations and regulatory action

The CHM advised new risk minimisation measures for the affected lidocaine products to improve safe use.

It was 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. The CHM recommended change of the legal status of oral lidocaine-containing products for teething from general sale (GSL) to pharmacy (P).

The indications, posology and safety warnings across all oral lidocaine products authorised for teething were recommended to be harmonised. The indication for use was re-positioning as second-line, after non-pharmacological approaches.

The pack size was recommended to be restricted to a maximum of 10 grams for oral lidocaine products authorised for teething.

Other oral, over the counter, lidocaine products for use in children for other indications, and oral lidocaine products licensed in adults, were updated to carry a warning against use in teething.

The MHRA announced the changes to the affected products in a Drug Safety Update on their website, including specific resources for pharmacists, parents, and caregivers.

(Public Assessment Report available in Annex 1)

Comments: There are a range of lidocaine-containing gels available for infant teething and other indications in the UK. The types of products available are similar to Medijel Gel in NZ.

The MHRA review only focused on infant teething products, and not lidocaine gels that may be used in children for other conditions, such as mouth ulcers.

While the MHRA review noted the lack of efficacy for use of lidocaine in infant teething, new risk minimisation measures were introduced for safety, mainly to reduce any potential risks of harm relating to overdose, medication error or accidental ingestion. These included restriction of indication of use to second line, change of classification, changes to directions for use, additional warnings, and smaller pack sizes.

4.4 European Medicines Agency (EMA), European Union

Public Assessment Report for paediatric studies submitted in accordance with Article 45 of Regulation (EC) No1901/2006 [47]

This Public Assessment Report, completed by the EMA in 2013, reviewed studies related to the use of lidocaine as a local anaesthetic in children submitted by pharmaceutical companies for their products.

This summary will focus on preparations for use in the mouth.

Dynexan 2% gingival paste

Dynexan 2% gel is only approved in two EU-countries: Germany and France.

The indications and age for use are different. In Germany, Dynexan is used in children under 6 years of age, whereas in France it is used in children 6 years and above.

Efficacy

Comparative clinical trial investigating Dynexan 2% gingival paste against placebo

This study was a double-blind, randomised, placebo-controlled design with two parallel arms. Children aged 6 – 15 years presenting with pain and mucosal lesions of the buccal cavity of requiring local anaesthesia as prevention of pain caused by dental or surgical procedures were included.

The primary endpoint was difference in pain intensity before and after treatment, as measured by the child, using a visual analogue scale. Secondary endpoints were tolerance as measured by frequency off allergic or local reactions in the region of application, and difference in pain intensity before and after treatment as assessed by the dentist.

64 subjects (33 placebo and 31 Dynexan) were randomised. Baseline characteristics were comparable, and mean age was 10.2 years in both groups. The most common indication for local anaesthesia was placement of dental clamps, which was comparable between the two groups. Pre-treatment pain intensity levels were also comparable between the two groups, as assessed by the child using VAS.

Pre-treatment intensity was assessed at baseline (T0) for the group of subjects presenting with pain and mucosal/buccal lesions. Post-treatment pain intensity was measured three minutes after the end of gel application (T2). In the dental/surgical procedure group, pain intensity was assessed after placement of dental clamp (T1). The clamp was then removed, and gel applied. Three minutes after the end of gel application the clamp was reintroduced, and pain intensity assessed (T2).

There was a statistically significant difference in pain intensity reduction between the two groups. The Dynexan group showed a mean intra individual VAS pain reduction of 19.7±18.3 (representing a 50% reduction from baseline) as compared to 7.6±22.6 (10% reduction) in the Placebo group. No local or general reactions were reported in any of the treatment groups.

A randomised, double blind, parallel groups, comparative, placebo-controlled pilot study to evaluate the efficacy and tolerability of Dynexan A Gel in infants with teething troubles and to develop assessment criteria and reactions for a further study based on the children's various behaviours

This study was a randomised, double-blind, comparative, placebo-controlled phase IV study in infants aged 6 – 12 months with pain in the region of the tooth with visible tooth tips and/or visibly discoloured, bleeding gingival.

The outcomes were assessment of efficacy and tolerability by the parents and by the investigator, assessment of symptoms of teething by parents and the investigator and nature and severity of adverse events. A pea-sized amount of gel was applied to the fingertip and rubbed on to the gingiva, for a maximum of four times daily for a total of 8 applications or 5 days.

A total of 25 patients were included in the study, however only 13 patients had available data. It was concluded by the sponsor that the conclusions about the therapeutic effect could only be made with some reservations. The observations suggested a trend towards a fast onset of action of Dynexan A Gel and a calming of children after administration of treatment. Regarding safety, the patients mainly showed symptoms commonly occurring concomitantly with teething, including vomiting, diarrhoea or retching.

Safety

There were no obvious safety concerns related to oral lidocaine-containing gel that were identified in the two studies, with a relatively small number of children, or in a safety investigation based on prescription data or a Periodic Benefit Risk Evaluation Report 2007 and 2009.

Concerning the overall conclusions on safety, published information is available concerning lidocaine use in small children and possible toxicity. Topical use of lidocaine can be associated with safety problems, particularly in small children, infants and babies who may be more sensitive to adverse events for example, CNS toxicity. The use of lidocaine on mucous membranes is also expected to be associated with a risk of higher systemic absorption compared to administration on intact skin.

Conclusions

On review of the submitted studies, the first study had an adequate design and an effect in pain intensity reduction versus placebo was shown. The second study was very small and not considered to contribute to the overall assessment of the product.

The sponsor of Dynexan gel was asked to justify the use of the gel in children under six years of age, as it was concluded that there is no pivotal clinical trial data available to support the use of Dynexan 2% in small children. The sponsor stated that the clinical usage of Dynexan is well established in children under six years of age, and there are no established safety concerns of note.

Updates to the SmPC to specify the age groups for use was proposed.

No changes to the current indications and doses of Dynexan in Germany or France were proposed. However, it was noted that while the product is not approved in other countries in the EU, use of the product for teething, may not be appropriate.

Comments: This public assessment report highlighted that there is no clinical data to support the use of Dynexan in children under six years of age. The use of this product for this indication was questioned by the assessor, however, no regulatory action was taken.

4.5 Therapeutic Goods Administration (TGA), Australia

4.5.1.1 Changes to Required Advisory Statements for Medicine Labels (RASML) [33]

The TGA initiated a safety investigation examining use of 2% lidocaine viscous in infants and children following safety review outcomes by Health Canada and FDA.

In 2021, the TGA undertook a consultation on addition of a proposed new required advisory statement for labels of non-prescription medicines containing more than 1.5 percent lidocaine for topical oral use.

The required advisory statement 'Do not use for teething pain in children' was proposed to ensure that consumers and healthcare professionals are aware that these medicines are not suitable for use for teething in children. Following the consultation, the new advisory statement was introduced.

Comments: Oral lidocaine-containing products, available over the counter, are not recommended for use in infant teething in Australia.

The Label Statements Database (LSD) contains information on warning statements for products in New Zealand. There are currently no statements required for non-prescription lidocaine products.

Of note, some products in NZ do include 'Do not use for teething pain in children' resulting from harmonisation with Australian labelling.

4.6 Summary (regulatory action)

Safety reviews of lidocaine viscous 2% solution identified a link between these products and severe adverse reactions, including seizures and cardiac problems, in younger children and infants.

The majority of cases identified related to overdose, for example due to medication error or incorrect administration, or by accidental ingestion. In some cases, the outcome was fatal.

Due to the risks of toxicity, use of lidocaine viscous 2% solution is not recommended for use in infant teething. It should only be used in other indications if clearly needed, and if there are no safer alternatives available. If used, doses and administration should follow recommended instructions. The FDA and Health Canada have previously published safety communications about this topic.

The MHRA review of oral lidocaine teething products identified these products could put patients at risk of potential harm and took action to reduce possible risks related to excessive exposure and incorrect product use.

The potential lack of good evidence for lidocaine in teething was commented on within the MRHA review and EMA report.

Australia requires lidocaine containing gels/solutions containing more than 1.5% lidocaine to have a warning statement that the product should not be used in infant teething.

Comments: Safety reviews by overseas regulatory authorities have identified risks of use of oral lidocaine in younger children and infants, and the importance of using these products as per the approved uses.

Medsafe has not previously communicated this safety concern. The data sheet for Xylocaine Viscous does contain information related to the post market paediatric reports.

The safety review by the FDA and Health Canada specifically reviewed lidocaine viscous 2% solution. A question to ask is if the identified risks can be extrapolated to other lidocaine products used within the mouth such as lidocaine gels and lower strength infant teething gels. Lack of appropriate directions for use or information of package labels/data sheets would be a factor, given the risk of toxicity is dose dependent.

4.7 Spontaneous reports

4.7.1 Company reports

[redacted]

4.7.2 CARM data

The Centre for Adverse Reactions (CARM) data was searched for any reports relating to use of oral mucosal lidocaine in younger children and infants.

As of 11 July 2023, there have been no relevant reports with this search criteria.

4.7.3 International reports

On 20 August 2023, the Australian Database of Adverse Event Notifications (DAEN) was reviewed for any reports of oral lidocaine-containing products that may be a result of toxicity in younger children and infants [48].

Table 10 highlights two reports identified that may correspond to toxicity.

Table 10: Oral lidocaine-containing product reports possibly relating to toxicity in younger children and infants, as per Database of Adverse Event Notifications

Gender	Age	Medicines	MedDRA reaction term
Male	<1	Mucosoothe (suspected)	Accidental overdose Somnolence Tremor
Male	5	Omeprazole (suspected) Xylocaine Viscous (suspected)	Chest pain Dyspneoa Pain

Source: Therapeutic Goods Administration. Database of Adverse Event Notifications (DAEN) – medicines. URL: https://daen.tga.gov.au/medicines-terms-condition/ (accessed 20 August 2023).

Comments: There have been no cases of adverse reactions associated with oral lidocaine-containing products in younger children or infants reported to CARM.

[redacted]

A low number of potential cases related to toxicity have been reported in Australia.

This is similar to the MHRA review which noted a low number of adverse reactions reported, despite potential widespread use of lidocaine teething gels/solutions.

4.7.4 New Zealand Poisons Centre

As part of this report, 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 three years.

A total of nine exposures were identified within the time period, and all were ingestions. Further information about the cases is outlined in Figure 5.

Figure 5: 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.

Four patients ingested at least half a tube of a product, and four patients reached the intervention level (referral to medical assessment) of 6mg/Kg lidocaine ingested. All patients were asymptomatic at the time of contact with the NPC. There are too few cases to be able to comment on any trends over time from the number of exposures. (Full report – see Annex 2).

Comments: 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.

Some ingestions were over the limit where a patient will likely be sent for medical assessment. At the time of contact with NPC, all patients were asymptomatic. It is not known if the child went on to experience any serious adverse reactions, such as seizures.

The reports highlight the importance of keeping medicine away from younger children. There are currently warnings on the NZ product labels that would inform caregivers or parents the potential for serious adverse reactions following unintentional exposure.

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.

The MHRA review also highlighted calls to NPIS relating to accidental exposure or therapeutic error.

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

5 DISCUSSION AND CONCLUSIONS

Oral lidocaine products, such as gels and solutions, have been linked to serious adverse reactions, including seizures and cardiovascular events, when administered incorrectly in younger children and infants. While uncommon, systemic toxicity from orally ingested viscous lidocaine is a potentially devastating complication of overdose.

Previous safety communications have been published by the FDA and Health Canada in relation to use of lidocaine viscous 2%. The MHRA have taken regulatory action for lidocaine-containing products used in infant teething. Regulatory action has also been taken by the TGA.

In NZ, there are several lidocaine containing products available that may be used in younger children and infants, where systemic absorption may occur. As toxicity is dose dependent, accurate dosing and administration to younger children and infants is required. Products available should have appropriate directions for use and warnings to minimise any potential risks.

Several concerns were highlighted in this paper that may increase risks of excessive or prolonged use, or medication errors with oral lidocaine-containing products in NZ. Current measures, such as directions for use, dosing, administration, and warnings may not be sufficient to be prevent risk of severe adverse reactions. In addition, affected products are classified as general sale or pharmacy only, which means that they may be brought OTC without the input of a healthcare professional.

Examples of possible risk minimisation measures that could be considered for affected products may include review of indications and/or directions for use, changes to the datasheet, publication of a data sheet or package label, addition of warnings to package labels (Label Statement Database consultation) or changes to classification.

Clinicians should be aware of the potential for intoxication and reserve topical anaesthetics for situations where they are absolute necessary, especially in younger children and infants. The Xylocaine Viscous data sheet notes that use in younger children should only occur if clearly needed, including where safer alternatives are not available or have been tried but failed. This information is only included in the data sheet. Mucosoothe, the funded product, does not have a published data sheet, and restriction of use in younger children and infants is not currently included on the package label.

The risk of harm may outweigh the benefits of use in some clinical situations for use in younger children and infants. Depending on the clinical situation, safer alternatives for younger children and infants age may need to be considered. Whether lower strength (< 1%) lidocaine gels should be used in infant teething is conflicting. While these products are available in pharmacies only in the UK, some other countries such as the US and Australia do not recommended lidocaine for use in teething, referencing clinical guidelines.

Indications and clinical setting for use likely also impact potential for toxicity. For example, risks associated with single dose use prior to pain provoking procedures such as within dentistry or in hospital, versus possibly repeated administration for pain relief associated with conditions such as mouth ulcers or infant teething.

Lidocaine is a medicine that has been approved for a long time, including gel and solution products. While oral lidocaine-containing products may be widely used, their efficacy may be limited.

Caregivers and parents should be informed of potential risks related to excessive use and the importance of following the dosage recommendations. 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 gels/solution is used than should be or if accidental ingestion were to occur.

6 ADVICE SOUGHT

The Committee is asked to advise:

- Is there a potential for oral lidocaine-containing products to cause toxicity in younger children and infants in New Zealand?
- If yes, does this apply to all oral lidocaine-containing products irrespective of strengths?
- Is regulatory action required to reduce potential risks of harm that affected products may pose within this age group (noting that different risk minimisations measures may be required depending on the product (i.e., Xylocaine Pump spray, Xylocaine Viscous, Mucosoothe, Lidocaine Gel 2%, Xylocaine Jelly, Medijel Gel))?
- Is further communication needed for this topic, other than MARC's Remarks?

7 ANNEXES

Annex 1: MHRA UK Public Assessment Report (December 2018) – Oral lidocaine products: risk minimisation measures for use in teething.

Annex 2: New Zealand National Poisons Centre regarding exposures to specific products with lidocaine 2018 – 2023

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