



# Oral lidocaine products: risk minimisation measures for use in teething

MHRA UK Public Assessment Report

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## 1. Introduction

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

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

## 2. Background

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

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

## 3. Teething in children

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

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

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

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

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

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

#### 4. Evidence

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

##### Efficacy (how well it works)

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

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

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

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

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

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

## Safety

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

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

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

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

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

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

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

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

## Discussion of efficacy and safety data

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

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

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

## **5. Expert advice**

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

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

## **6. MHRA action**

In December 2018, the MHRA announced the comprehensive package of measures set out in the advice from the CHM. The Drug Safety Update article is available on the MHRA website:

<https://www.gov.uk/drug-safety-update/oral-lidocaine-containing-products-for-infant-teething-only-to-be-available-under-the-supervision-of-a-pharmacist>

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## **Glossary:**

### **General Sales List medicine**

Medicines that can be bought from any shop without a prescription

### **Labelling**

Information on the immediate or outer packaging of a medicine

### **Lidocaine**

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

### **Marketing authorisation holder**

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

### **National competent authority**

A medicines regulatory authority in a European Union Member State

### **Pharmacy medicine**

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

### **Risk minimisation measure**

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