

**Public Assessment Report
for paediatric studies submitted in accordance
with Article 45 of Regulation (EC) No1901/2006, as
amended**

**Cathejell Lidocaine, Dynexan, EMLA, Jelliproct, Orofar,
Strepsil Plus, Xylestesin-A, Xylonor
(Lidocaine)**

SE/W/008/pdWS/001

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ADMINISTRATIVE INFORMATION

Invented name of the medicinal product(s):	See section VI
INN (or common name) of the active substance(s):	Lidocaine
MAH (s):	See section VI
Pharmaco-therapeutic group (ATC Code):	N01BB52 C05AA61 J01RA R02AA R02AA20 A01AB14 A01AE11
Pharmaceutical form(s) and strength(s):	See section IV, Annex II

I. EXECUTIVE SUMMARY

SmPC and PL changes are proposed, mainly in SmPC sections 4.1 and 4.2.

Summary of outcome

- No change
- Change
- New study data: N/A
- New safety information: N/A
- Paediatric information clarified: mainly section(s) 4.1 and 4.2
- New indication: N/A

II. RECOMMENDATION¹

Based on the data submitted, the MAHs are encouraged to submit a Type IB variation application by May 1st 2013.

III. INTRODUCTION

Eight MAHs submitted a large number of completed paediatric studies for lidocaine, in accordance with Article 45 of the Regulation (EC) No 1901/2006, as amended, on medicinal products for paediatric use.

Lidocaine is an old and well-established substance used as a local anaesthetic since the 1940ies. Lidocaine is also used as a class IB antiarrhythmic agent. This procedure concerns only studies related to the use of lidocaine as a local anaesthetic, i.e. not as an antiarrhythmic medicinal product. In most of the products concerned, lidocaine is used in combination with other substances. Thus, this procedure concerns a variety of nationally approved products, formulations and different indications with large regional differences within EU and the following table summarizes the information for different products.

Product name and form	MAH	Active substance(s)	Indication(s)/Approved age range
Xylestesin-A , solution for injection	3M ESPE AG, Germany	Lidocaine hydrochloride, epinephrine (adrenaline) hydrochloride	Infiltration- and nerve block anaesthesia in dentistry /No age range given (dose recommendations from 20 kg; no more than 5 mg lidocaine per kg body weight should be injected in children)
EMLA , cream and medicated plaster	AstraZeneca (CANA Pharmaceutical Laboratories in Greece)	Lidocaine hydrochloride, prilocaine hydrochloride	Topical anaesthetic of the skin in connection with needle insertions and superficial skin surgery/ 0 (neonates) -11 years
Jelliproct , ointment and suppositories	Grüntentahl	Lidocaine hydrochloride, fluocinonide	For short-term symptomatic treatment of inflammatory diseases in the area of the anus, especially haemorrhoids, proctitis and anal eczema. Application in connection with proctological interference. / No specific paediatric posology. Twice daily application, duration 1-2 weeks
Dynexan 2% , gingival paste	Kreussler Pharma	Lidocaine hydrochloride	Temporary treatment of pains at the oral mucosa, gingiva, and lips. / Approved for use in children and infants in DE, from 6 years in FR
Cathejell Lidocaine , gel for intraurethral instillation	Montavit	Lidocaine hydrochloride, chlorhexidine hydrochloride	Not specifically outlined by the MAH (Described as reduction of pain during catheterization and prevention of onset of urinary tract infections following transurethral procedures)

¹ The recommendation from section V can be copied in this section.

Orofar , lozenge, gelsollet, spray and Solution	Novartis	Lidocaine HCl and Benzoxonium chloride	Sore throat associated with colds, pharyngitis or laryngitis; stomatitis, aphtous ulcers, gingivitis; adjuvant in tonsillitis; treatment of dental plaque (oral solution). /Children and adolescents aged 4 years and above.
Strepsils Plus , lozenges	Reckitt Benckiser	lidocaine hydrochloride, amylmetacresol, dichlorobenzyl alcohol	Symptomatic relief of mouth and throat infections including severe sore throat./ Children and adolescents aged over 12 years.
Xylonor , solution for injection, gel, solution	Septodont	Lidocaine hydrochloride, adrenaline hydrochloride, Lidocaine hydrochloride, noradrenaline hydrochloride, Lidocaine hydrochloride, cetrimide	Not specifically outlined by the MAH (Described as regional and local anaesthesia)

Short critical expert overviews were provided from all MAHs.

Most MAHs stated initially that the submitted paediatric studies do not influence the benefit risk for their products and that there is no consequential regulatory action. Nevertheless, during the procedure a number of proposals to modify the SmPC have been made by the MAHs.

In addition, the following documentation has been included as per the procedural guidance:

- A line listing
- An annex including SmPC wording of sections 4.1 and 4.2 related to the paediatric use of the medicinal product, and related PL wording

IV. SCIENTIFIC DISCUSSION

IV.1 Information on the pharmaceutical formulation used in the clinical study(ies)

This paediatric procedure covers a range of different pharmaceutical formulations (refer to table above). Formulations specific to paediatric use are generally not available.

IV.2 Non-clinical aspects

Most of the MAHs did not submit any non-clinical data.

For Cathejell Lidocaine (Montavit), one non-clinical study was submitted by the MAH. The relative CNS and cardiovascular toxicity of lidocaine was compared in ten adult sheep, ten newborn lambs, nine pregnant ewes and their foetuses during continuous infusion of lidocaine into the jugular vein (2 mg/kg/min) by Morishima et al. The result indicated that fetal and newborn lambs are no more sensitive to lidocaine toxicity than are adult sheep.

The lack of non-clinical data is acceptable since lidocaine is a well known substance.

IV.3 Clinical aspects

1. Introduction

The studies have been summarized below for each respective MAH.

3M ESPE AG

1. Introduction

The product Xylestesin-A is a solution for injection containing Lidocaine hydrochloride 20 mg/ml and (R)-Epinephrine hydrochloride 0.015 mg/ml. The indication is Infiltration anesthesia and nerve-block in dentistry. The dosage should be individually determined from case to case depending on the method used and special characteristics of the particular case.

Doses of 1-4 ml are sufficient for young persons over 15 years of age and adults. In children weighing about 20 - 30 kg, doses of 0.25 - 1 ml are sufficient; and in children weighing 30 - 45 kg, 0.5 - 2 ml. No more than 5 mg lidocaine per kg body weight should be injected in children.

No changes in the currently approved SmPC were proposed.

The MAH submitted 11 publications from controlled clinical studies with lidocaine HCl 20 mg/ml and epinephrine HCl 0.015 mg/ml products used in dentistry. In the cover letter, the MAH of Xylestesin-A points out that the studies were not performed with this particular product since Xylestesin-A is a generic product.

2. Clinical study(ies)

For simplicity, the studies are presented in the following tables (Table A description of studies; table B study results) and comments are given below.

No pharmacokinetic or pharmacodynamic studies were presented in paediatric patients.

➤ Methods

Table A Description of clinical efficacy and safety studies

Study ID	Number of study centers Location(s)	Study start Enrolment status, date Total enrolment/Enrolment goal	Design Control type	Study & Ctrl Drugs Dose, route & Regimen	Study Objective	# subjects by arm entered / completed	Duration	Gender M/F Median age (Range)	Diagnosis Inclusion Criteria	Primary Endpoint(s)
Placebo control										
[Coulthard et al. 2006 ⁶]	No detail UK	No detail	r, controlled	T: LID 2% + EPI 1:200,000 2ml (local anaesthesia) C: P (0.9% sodium chloride) 2ml Buccal infiltration: intraoral injection after induction of anaesthesia	Study the efficacy + safety	142/139 T: 71/70 C: 71/69	Single dose	73m, 66f; median 6y	Pat. =12y scheduled for dental extractions under general anaesthesia	Pain scores
No-treatment control										
-										
Dose-response (includes studies comparing anaesthesia techniques with the same anaesthetic doses)										
[College et al. 2000 ⁵]	3 USA	No detail	p	LID 2% with EPI 1:100,000 (97% of pat.) or MEPI 2% with 1:20,000 levonordefrin (2% of pat.) T1: bilateral mandibular block anaesthesia T2: unilateral mandibular block anaesthesia	Evaluate the efficacy	320 T1: 157 T2: 163	Single doses	18M-18y 167f, 153m	Paediatric pat. planned for operative treat. requiring mandibular block anaesthesia	Postoperative soft tissue trauma
[Ashkenazi et al. 2006 ¹]	2 Israel	No detail	No detail	LID 2% with EPI 1:100,000 (Octacain) 0.9ml (max. dose: 4.4mg/kg BW)	Compare the efficacy	178 T1: 122 T2: 56	Single dose	2-14y (mean 6.8±2.8y)	Paediatric pat. requiring	Pain behavior (using
Study ID	Number of study centers Location(s)	Study start Enrolment status, date Total enrolment/Enrolment goal	Design Control type	Study & Ctrl Drugs Dose, route & Regimen	Study Objective	# subjects by arm entered / completed	Duration	Gender M/F Median age (Range)	Diagnosis Inclusion Criteria	Primary Endpoint(s)
				T1: local infiltration (buccal or palatal) with the use of a CDS T2: intrasulcular injection with the use of a CDS				93m, 85f	local anaesthesia to primary maxillary molars	Children's Hospital of Eastern Ontario pain scale CHEOPS range 4-13)
[Baghdadi 2000 ²]	No detail	No detail	r, splitmouth study design	T: LID 2% with EPI 1:80,000 (Lidocaton™) R: Electronic dental anaesthesia (EDA; 3M dental electronic anaesthesia system No. 8670)	Compare the efficacy	108/100	Single dose	6-12y (mean 9.1±1.8y) 34m, 74f	Paediatric pat. undergoing restorative procedures	Pain levels (using color scale)
[Naidu et al. 2004 ¹⁰]	1 USA	No detail	r, controlled, blinded	LID 2% with EPI 1:100000 1.8ml T1: infiltration/ intrapapillary injection anaesthesia T2: inferior alveolar block/ long buccal infiltration anaesthesia	Compare the efficacy	101 T1: 49 T2: 52	Single dose	5-8y (mean 78±12M) 55f, 46m	Paediatric pat. who need a pulpotomy treat. + stainless steel crown placement in a lower primary molar	Pain levels (using the color analogue scale)
[Oulis et	No detail	No detail	Open,	LID 2% with EPI 1:100000	Compare	89	Single	3-9y	Paediatric	Pain

Study ID	Number of study centers Location(s)	Study start Enrolment status, date Total enrolment/Enrolment goal	Design Control type	Study & Ctrl Drugs Dose, route & Regimen	Study Objective	# subjects by arm entered / completed	Duration	Gender M/F Median age (Range)	Diagnosis Inclusion Criteria	Primary Endpoint(s)
al. 1996 ^{11]}			half-mouth study design	1.7ml (Xylestesin forte, ESPE Seefeld) T1: mandibular infiltration T2: mandibular block	the efficacy		dose	42m, 47f	pat. requiring treat. on contralateral primary mandibular molars ¹	evaluation (pain scale)
[Wilson et al. 1990 ^{16]}	1 USA	No detail	db	T1: LID 2%/ EPI 1:100000 mandibular teeth: 1.5ml, maxillary teeth: 0.8ml T2: LID 1%/ EPI 1:100000 mandibular teeth: 1.5ml, maxillary teeth: 0.8ml	Compare the clinical efficacy	34 T1: 18 T2: 16	Single dose	4.5-10.5y T1: 9m, 9f; mean 96±21M T2: 8m, 8f; mean 88±19M	Restorative + surgical procedures on primary molars in paediatric pat.	Pain report by pat. (using "faces" scale)
Active control										
[Sammons et al. 2007 ^{14]}	No detail	No detail	r, controlled, sb	T: LID 2% with EPI 1:80,000 intraligamental (each primary tooth 0.15ml; max. total dose: 2ml) R: standard treatment (postoperative codeine pain relief as required)	Evaluate the efficacy	86/85 T: 42/41 R: 44/44	Single dose	47m, 38f	Primary teeth extraction under general anaesthesia	Pain score (using Toddler-Preschooler postoperative pain scale)
[Malamed et al.	7 USA, UK	No detail	r, db, parallel-	T: LID 2% with EPI 1:100,000	Compare the	70 T: 20	Single dose	All <13y T: 13f, 7m	Paediatric dental pat.	Pain score (VAS)

¹ includes class I and II amalgam restorations, stainless steel crowns, formocresol pulpotomies, extractions

Study ID	Number of study centers Location(s)	Study start Enrolment status, date Total enrolment/Enrolment goal	Design Control type	Study & Ctrl Drugs Dose, route & Regimen	Study Objective	# subjects by arm entered / completed	Duration	Gender M/F Median age (Range)	Diagnosis Inclusion Criteria	Primary Endpoint(s)
2000 ^{7]}			gr., mc, active-controlled	R: ART 4% with EPI 1:100,000 Lowest effective dose (anaesthesia) administered as submucosal infiltration and/or nerve block (total dose was not to exceed 7.0mg/kg BW)	efficacy + safety	R: 50		R: 21f, 29m	undergoing general dental procedures	
[Ram et al. 2006 ^{13]}	2 Israel	No detail	r, co	T: LID 2% with EPI 1:100,000 (Octocaine®, Novocol Pharmaceutical of Canada Inc. Cambridge, Canada) R: ART 4% with EPI 1:200,000 (Ubistesin, ESPE Dental AG, Germany) Up to 1 cartridge was administered (max. dose: T: 4mg/kg BW; R: 5mg/kg BW)	Evaluate + compare the efficacy	62 ²	Single doses	34f, 28m Mean 8.4±2.3y (5-13y)	Dental operative procedures preceded by local anaesthesia	Pain score (modified Taddio's behavioural pain scale)
[teDuits et al. 1993 ^{15]}	1 USA	No detail	Open, r	T: LID 2% with EPI 1:100,000 (local anaesthesia; Xylocaine®) R: Electronic dental	Compare the efficacy	27	Single dose	6-12y	Restorative dental procedures (preventive)	Pain perception scores (using

² included 40 maxillary local infiltrations and 22 mandibular block injections

Study ID	Number of study centers Location(s)	Study start Enrolment status, date Total enrolment/Enrolment goal	Design Control type	Study & Ctrl Drugs Dose, route & Regimen	Study Objective	# subjects by arm entered / completed	Duration	Gender M/F Median age (Range)	Diagnosis Inclusion Criteria	Primary Endpoint(s)
				anaesthesia (EDA; Spectrum Max-SD®) by transcutaneous electrical nerve stimulation					resin restoration)	Eland Color Scale)
<i>External (Historical) control</i>										

- Study design

Of the 11 published studies, one was a placebo-controlled study, six were comparative studies assessing dose-response and different administration routes and four were active-controlled studies. The studies were generally single-blind or open.

- Study populations

Male and female children and adolescents undergoing different dental procedures were included in the studies. The age ranged from 1.5 to 18 years, with the majority of patients being 4-10 years old. The inclusion criteria differed across studies, but dental extractions and restorative procedures on primary molars were frequent causes for the use of local anaesthesia.

- Treatments

Lidocaine 2% with epinephrine (1:80 000 up to 1: 200 000) was used at typical doses, mainly for infiltration and conduction anaesthesia.

Reference treatments were codeine (for prevention of post-operative pain), articaine 4% with epinephrine and electric dental anaesthesia.

- Outcomes/endpoints

Pain and pain behaviour measured by different scores were primary outcomes for assessment of efficacy.

➤ **Results**

- Efficacy results

Efficacy results are summarized in Table B.

Table B Results of efficacy studies

Study	Treatment arm	# Enrolled/ Completed	Endpoints		Primary Endpoint change	Statistical test/ P value	Secondary Endpoint change
			Primary	Secondary			
Placebo control							
[Coulthard et al. 2006 ⁶]	T: LID 2% + EPI 1:200,000 2ml (local anaesthesia) C: P (0.9% sodium chloride) 2ml Buccal infiltration: intraoral injection after induction of anaesthesia	142/139 T: 71/70 C: 71/69	Pain scores (Five face scale)	Mean distress scores	T=C (preoperatively, on waking from the general anaesthesia, at 30min. postoperatively or at 24h)	-	T=C (on waking from the general anaesthesia and at 30min.)
No-treatment control							
-							
Dose-response (includes studies comparing anaesthesia techniques with the same anaesthetic doses)							
[College et al. 2000 ⁷]	LID 2% with EPI 1:100,000 (97% of pat.) or MEPI 2% with 1:20,000 levonordefrin (2% of pat.) T1: bilateral mandibular block anaesthesia T2: unilateral mandibular block anaesthesia	320 T1: 157 T2: 163	Postoperative soft tissue trauma	-	T1>T2 (for pat. <4y: 5% vs. 35%) T1>T2 (for all pat.: 11% vs. 16%)	P<0.02 NS	-
[Ashkenazi et al. 2006 ¹]	LID 2% with EPI 1:100,000 (Octacain) 0.9ml (max. dose: 4.4mg/kg BW) T1: local infiltration (buccal or palatal) with the use of a CDS T2: intrasulcular injection	178 T1: 122 T2: 56	Pain behavior (using Children's Hospital of Eastern Ontario pain scale CHEOPS range 4-13)	Overall effectiveness	T1=T2 (T1 palatal: 6.0±1.9 vs. T1 buccal: 5.8±1.7 vs. T2: 5.9±1.6)	-	T1=T2 (85% vs. 88%, NS)

Study	Treatment arm	# Enrolled/ Completed	Endpoints		Primary Endpoint change	Statistical test/ P value	Secondary Endpoint change
			Primary	Secondary			
	with the use of a CDS						
[Baghdadi 2000 ²]	T: LID 2% with EPI 1:80,000 (Lidocaton™) R: Electronic dental anaesthesia (EDA; 3M dental electronic anaesthesia system No. 8670)	108/100	Pain levels (using color scale)	Behavior (using sound, eye, motor (SEM) scale)	T>R	NS	T>R (NS) (63% of pat. preferred R, 30% preferred T, 1.9% preferred both, 7.3% showed intolerance to R)
[Naidu et al. 2004 ¹⁰]	LID 2% with EPI 1:100000 1.8ml T1: infiltration/ intrapapillary injection anaesthesia T2: inferior alveolar block/ long buccal infiltration anaesthesia	101 T1: 49 T2: 52	Pain levels (using the color analogue scale)	Supplemental local anaesthetic requirements	T1>T2	NS	T2>T1 (7.7% vs. 10.2%; P=0.07)
[Oulis et al. 1996 ¹¹]	LID 2% with EPI 1:100000 1.7ml (Xylestin forte, ESPE Seefeld) T1: mandibular infiltration T2: mandibular block	89	Pain evaluation (using sounds, motor, ocular changes indicating pain scale)	Behavior evaluation (using Frankl Behavior Rating Scale)	T1=T2 (for performing amalgam or stainless steel crown restorations) T2>T1 (for pulpotomy and extraction)	NS P=0.05	T1=T2 (for performing amalgam or stainless steel crown restorations or extractions) T2>T1 (for removal of coronal pulp)
[Wilson et al. 1990 ¹⁶]	T1: LID 2%/ EPI 1:100000 mandibular teeth: 1.5ml, maxillary teeth: 0.8ml T2: LID 1%/ EPI 1:100000 mandibular teeth: 1.5ml, maxillary	34 T1: 18 T2: 16	Pain score, reported by pat. (using "faces" scale)	Anaesthetic failures	T1=T2	NS	T1>T2 (2 failures vs. 5 failures)

Study	Treatment arm	# Enrolled/ Completed	Endpoints		Primary Endpoint change	Statistical test/ P value	Secondary Endpoint change
			Primary	Secondary			
	teeth: 0.8ml						
Active control							
[Sammons et al. 2007 ¹⁴]	T: LID 2% with EPI 1:80,000 intraligamental (each primary tooth 0.15ml; max. total dose: 2ml) R: standard treatment (postoperative codeine pain relief as required)	86/85 T: 42/41 R: 44/44	Pain score (using Toddler-Preschooler postoperative pain scale)	Analgesic use (at home)	At 5min.: T>R At 15-, 30-, or 60min.: T=R	P=0.023	T=R
[Malamed et al. 2000 ⁷]	T: LID 2% with EPI 1:100,000 R: ART 4% with EPI 1:100,000 Lowest effective dose (anaesthesia) administered as submucosal infiltration and/or nerve block (total dose was not to exceed 7.0mg/kg BW)	70 T: 20 R: 50	Pain score (VAS in cm)	-	R>T (Investigator's score: complex procedure: 0.6 vs. 2.8; Patient's score: complex procedure: 1.1 vs. 2.3)	NS	-
[Ram et al. 2006 ¹³]	T: LID 2% with EPI 1:100,000 (Octocaine®, Novocol Pharmaceutical of Canada Inc. Cambridge, Canada) R: ART 4% with EPI 1:200,000 (Ubistesin,	62 ³	Pain score/reaction (modified Taddio's behavioural pain scale)	Duration of numbness of soft tissues	T=R	-	R>T (3.43±0.7h vs. 3.0±0.8h; P=0.003)

³ included 40 maxillary local infiltrations and 22 mandibular block injections

Study	Treatment arm	# Enrolled/ Completed	Endpoints		Primary Endpoint change	Statistical test/ P value	Secondary Endpoint change
			Primary	Secondary			
	ESPE Dental AG, Germany) Up to 1 cartridge was administered (max. dose: T: 4mg/kg BW; R: 5mg/kg BW)						
[teDuits et al. 1993 ¹⁵]	T: LID 2% with EPI 1:100,000 (local anaesthesia; Xylocaine®) R: Electronic dental anaesthesia (EDA; Spectrum Max-SD®) by transcutaneous electrical nerve stimulation	27	Pain perception scores (using Eland Color Scale)	-	T=R (78% of children preferred EDA)	NS	-
External (Historical) control							
-							

In the only placebo-controlled study submitted, there was no statistically significant difference in pain or distress scores between active treatment and placebo at different time points, e.g. preoperatively, on waking and at 30 min.

In the dose response studies, a number of different anaesthetic techniques and doses were compared. In many of these studies, no differences between treatments/ techniques were observed. Recommendations related to different anaesthetic techniques used in dental procedures are likely different across different MS and will not be further discussed within the scope of this procedure. Thus, the results were not reviewed in further detail in this report.

In the active comparator studies, comparisons were made vs. standard treatment with codeine used as rescue medication in one single-blinded trial, vs. articaine in two studies (one double-blind one single-blind) and vs. electronic dental anaesthesia in an open study. No difference vs. standard treatment was found in the study by Sammons et al. except very early after recovery

and no difference vs. lidocaine and electronic dental anaesthesia was observed in the open study by teDuits et al. Lidocaine and articaine appeared to equally effective.

Of the studies referred to above, several had limitations in their study design (e.g. open-label) and in several of them efficacy of lidocaine in dental procedures in children or adolescents could not be confirmed. As pointed out by the MAH, several factors may influence the anaesthetic efficacy of local anaesthetics in dentistry, in adults as in children, e.g. administration techniques which may affect painfulness of administration. Even if the results are not very impressive, the data do not give any reason to change the current recommendations regarding the use of this product in children and adolescents.

- Safety results

Table C shows a summary of AEs in pooled placebo- and active controlled studies.

Table C Incidence of Adverse Events in Pooled Placebo and Active Controlled Trial Database

Study ID Treatment	Total Lidocaine with Epinephrine		Total Placebo		Total Reference treatment	
	153		71		112	
Body System/Adverse event (coded by MedDRA PT Preferred term)	N	%	N	%	N	%
Nervous system disorders						
Headache	0	0.000	0	0.000	1	0.893
Vascular disorders						
Haematoma	1	0.654	0	0.000	0	0.000
General disorders and administration site conditions						
Injection site pain	0	0.000	0	0.000	1	0.893
Pain	2	1.307	0	0.000	1	0.893
Injury and poisoning						
Procedural complication	5	3.268	1	1.408	2	1.786
Procedural pain	1	0.654	0	0.000	3	2.679
Total	9	5.882	1	1.408	8	7.143

A case report of a 4-year old child who developed a systemic anaphylactic reaction 15 min after receiving an intrapulpal injection of lidocaine HCl/epinephrine for a dental procedure was described (Chiu et al.). The child was referred to the ICU and needed mechanical ventilation but recovered completely and was discharged 4 days later.

Another study by Meechan et al investigated haemodynamic effects of lidocaine/epinephrine in comparison with prilocaine/felypressin, in a randomised, cross-over, single-blind design. Significant differences between the treatments were found and after administration of the lidocaine/epinephrine solution, there was an increase in heart rate 10 min after administration and a drop in diastolic blood pressure 20 min after administration.

A PSUR was also submitted covering a period between November 2005 and October 2008 and more than 81,000,000 cartridges were sold during this interval. The PSUR covers a total of 55 case reports of which 7 were classified as serious. Skin and subcutaneous disorders, respiratory, eye, nervous system and immune system disorders were most commonly reported.

The incidence of AEs was rather similar for lidocaine/epinephrine and the reference treatment group. Hypersensitivity to local anaesthetic of the amide type and haemodynamic effects are not unknown events and are already labelled. The safety data presented do not give rise to any new

concerns in a paediatric population. The PSUR did not specify whether any of the reported AEs occurred in children or adolescents.

The maximum dosage for this product and similar products (Septodont/Xylonor) was discussed during the procedure. The maximum dose in dental use differed for these products, being 5 mg/kg for Xylestesin-A and 2.2 mg/kg for Septodont/Xylonor. Based on information submitted by the different MAHs and literature research by the Rapporteur it was concluded that the generally accepted recommended maximum dose for paediatric dental use reported in the literature is in the range of 4-5 mg/kg BW although the scientific basis for paediatric posology regarding dental injection lidocaine analgesia is not firm. There is no absolute contraindication for injectable analgesia in children below 4 years of age, even if it is mostly found not optimal.

The following posology for paediatric injectable analgesia is suggested:

SmPC section 4.2

<Product> is indicated in adults and children. Special care has to be exercised when treating children below 4 years. The quantity to be injected should be determined by the age and weight of the child and the magnitude of the operation. The anaesthesia technique should be selected carefully. Painful anaesthesia techniques should be avoided. The behaviour of the child during treatment has to be monitored carefully.

The average dose to be used is in the range of 20 mg to 30 mg lidocaine hydrochloride per session. The dose in mg of lidocaine hydrochloride which can be administered in children may alternatively be calculated from the expression: child's weight (in kilograms) x 1.33.

Do not exceed the equivalent of 5 mg of lidocaine hydrochloride per kilogram of body weight.

AstraZeneca

EMLA is available as a cream and as a patch containing both lidocaine HCl and prilocaine HCl in a eutectic mixture. The approved indications (in Sweden and, presumably, most EU MS) for EMLA cream are:

- Local anaesthesia of the skin prior to needle insertion, and superficial surgical procedures.
- Local anaesthesia of leg ulcers for cleaning and superficial surgical procedures such as removal of fibrin, pus and necrosis.
- Local anaesthesia on genital mucosa.

EMLA medicated plaster is indicated for local anaesthesia of the skin prior to needle insertion, and superficial surgical procedures (in Sweden and, presumably, most EU MS).

The MAH did not provide the posology for EMLA in the clinical overview and a SmPC was not submitted. The posology for EMLA cream in children in the Swedish SmPC is **1 g per 10 cm²** for use prior to needle insertion, and superficial surgical procedures. A thick layer of the cream should be applied under an occlusive bandage. The dose should not exceed 1 gram per 10 cm² and should be adjusted according to the application area:

- 0-3 months: up to 10 cm² (total 1 g) (maximum daily dose) for 1 hour;

- 3-12 months: up to 20 cm² (total 2 g) for 1 hour;
- 1-6 years up to 100 cm² (total 10 g) for 1 hour; up to 5 hours
- 6-12 years up to 200 cm² (total 20 g) for 1 hour; up to 5 hours

The posology for EMLA patch is 1 or several patches applied simultaneously for at least 1 hour in children aged 1-12 years. In children aged 3-12 months, 1 or at most 2 patches could be applied simultaneously for 1 hour.

In children aged 0-3 months, 1 patch is the maximum daily dose and it should not be applied for more than 1 hour. An application time of more than 5 hours does not result in improved anaesthetic effect.

Both for cream and patch, the recommendation in children with atopic dermatitis is to use a reduced application time (30 minutes).

No explicit changes in the currently approved SmPC were proposed by the MAH.

The MAH states that the majority of the study reports outlined in their overview have already been submitted to and assessed by the majority of the EU Member States with a national MA for EMLA (as demonstrated by their local labelling). However, some of the study reports have not previously been submitted to all Member States (although some), and a small minority of Member States have not previously received any of the study reports (despite having paediatric labelling – which implies that they may have received some reports, and records are possibly incomplete).

The MAH refers to a **Clinical overview 2006** (“The Clinical Overview EMLA® in Paediatrics; Use in Neonates and Infants and Recommended Posology for Paediatric Patients of All Age Groups”) produced to support the use of EMLA in a paediatric population, including neonates and infants. Since the studies and publications have been submitted to NCAs to support national MAAs, these studies were not reviewed in detail in this report.

Table 1 Overview of clinical studies included in **Clinical Overview 2006**, by indication

Investigator/ Report No.	Design	No of patients EMLA/ Placebo	Indication/ Study period	Results
Dillard et al 1996/ 802-540-LC-0107-01	Double-blind, randomised	36/32	Circumcision Mar 1994 – Feb1995	No significant difference between EMLA and placebo
Koren et al 1997/ 802-540-LC-0103	Double-blind, randomised	38/30	Circumcision Jan 1995 – Dec 1995	The overall pain associated with the circumcision was significantly lower in the EMLA group. The magnitude of the effect varied with the stage of the circumcision.
Kurien et al 1984/ 802-10 AC 022-1	Double-blind, randomised	27/28	Venipuncture 1983-1984	Significant effect of EMLA
Lindh et al 1999/ Not applicable	Double-blind, randomised	28/28	Venipuncture 1998	EMLA decreased the pain response during venipuncture in newborn infants
Merchant et al 1997/ 051-50	Double-blind, randomised	1/2	Venipuncture Mar 1996 – Apr 1996	No new safety signals were observed
Halperin and Houston 1998/ 802-540-LC-0122-01	Double-blind, randomised	80/80	Vaccination (s.c.) 15 Sep 1997 – 8 Apr 1998	Significant effect of EMLA
Halperin and Houston 1999/ 802-540-LC0145-01	Double-blind, randomised	82/83	Vaccination (i.m.) 18 Sep 1997 – 15 Feb 1999	Significant effect of EMLA in 6-month-old infants Trend towards significant effect of EMLA in 2- to 4-month-old infants No significant effect in less than 1-month-old neonates
Svenningsen et al 1997/ 802-540-LC-0104	Double-blind, randomised	25/25	Heel lancing Nov 1987 – May 1988	No significant difference between EMLA and placebo
Andréasson et al 1997/ 802-540-LC-0097	Double-blind, randomised	24/23	Safety Oct 1995 – Nov 1996	No new safety signals were observed
Engberg et al 1986/ 802-10 AC026	Open	22/-	Safety May 1984 – Sep 1985	No new safety signals were observed
Haugstvedt et al 1988a/ 802-10 AC069	Open	10/-	Safety Nov 1986 – Aug. 1987	No new safety signals were observed

Investigator/ Report No.	Design	No of patients EMLA/ Placebo	Indication/ Study period	Results
Haugstvedt et al 1988b/ 802-10 AC070	Open	10/-	Safety; Surgical removal of mollusca Nov 1986 – Jan 1988	No new safety signals were observed
Nilsson et al 1988/ 802-10 AC071 (part B)	Open	10/-	Safety May 1985 – Aug 1987	No new safety signals were observed
Nilsson et al 1989/ 802-10 AC071 (part C)	Open	4/-	Safety (Concomitant treatment with sulphonamides or nitrofurantoin) May 1985 – Aug 1987	No new safety signals were observed
Westgren and Danielson 1987a/ 802-10 AC037	Open	9/-	Safety Nov 1985 – Feb 1986	No new safety signals were observed
Westgren and Danielson 1987b/ 802-10 AC059	Open	10/-	Safety Oct 1986 – Feb 1987	No new safety signals were observed

In addition to the studies referred to in the Clinical Overview 2006 and summarized above, AstraZeneca sponsored additional studies in which paediatric patients were included. These studies are summarized below by different uses.

No pharmacokinetic or pharmacodynamic studies were presented in paediatric patients.

Venepuncture

Studies investigating the efficacy of EMLA in conjunction with venepuncture are summarised in Table 2.

**Table 2 EMLA efficacy studies not submitted in all EU member states:
Venepuncture**

Investigator/ Report No.	Design	Number of patients EMLA/ Placebo	Age	Sex (boys/ girls)	Dose/ treatment time/ area of application	Summary of results
Dangel et al 1998/MA-EMA- 0001	Double- blind, randomised, Placebo- controlled	62/59	7 to 15 yrs	73/48	Approx 2.5 g/60 to 90 min/ on the place selected for venepuncture	Significantly less pain scores with EMLA vs placebo
Maunuksela et al. 1986/ 802-10 AC030-1	Double- blind, randomised, placebo controlled	30/30	4 to 10 yrs	37/23	2g/ 60 min/ on the vein selected for cannulation	Significant alleviation of pain with EMLA vs placebo as judged by anaesthesiologists and patients
Hallen et al. 1983/ 802-10 AC015-2	Double- blind, randomised, placebo controlled	56/58	4 to 17 yrs	80/34	1 ml (50mg)/ short (20- 40min) or long (41-60 min)/ on top of a suitable vein	Cusum test showed pain relief with EMLA but not with placebo at the 60 min application time
Saukkonen and Wannerud 1983/ 802-10 AC013-2	Double- blind, randomised, placebo controlled	20/19	7 to 11 yrs	26/13	1-2 ml/ 60 min/ on the area selected for cannulation	Significantly lower pain scores with EMLA vs placebo
Ecoffey et al. 1992	Open, prospective	39/0	3m to 15 yrs	33/6	1.6±0.6g cream/ 30 min – 2hours/ not known	Children ≤5 yrs: Pain score 7.5±2.2 (CHEOPS 4-13 range) Children >5 yrs: Pain score 24±21 (VAS 0-100)

The MAHs conclusion based on the results of the studies summarised above was that EMLA cream was considered to provide convenient analgesia for venepuncture in toddlers and children. Pain relieving effect of EMLA, but not placebo, was achieved with a 60-minute application time.

These studies confirm the efficacy of EMLA in venepuncture in children and adolescents.

Needle insertion and vaccination

Studies investigating the efficacy of EMLA in conjunction with venepuncture and vaccination are summarized in Table 3.

Table 3 EMLA efficacy study not submitted in all EU member states: Needle insertion and vaccination

Investigator/ Report No.	Design	Number of patients EMLA/ Placebo	Age	Sex (boys/ girls)	Dose/ treatment time/ area of application	Summary of results
Walsh and Bertilson 1984 802-10 AC019-1	Double-blind, randomized	29/30	10 to 11 yrs	25/34	2.5 ml/ 60 minutes/ over injection site on upper arm	Significant reduction of pain for both needle insertion and vaccination

This rather small study supported that application of EMLA one hour before needle insertion and vaccination reduced pain associated with this procedure. Paleness of the skin occurred more frequently in the EMLA compared with the placebo group and redness of the skin occurred in a few EMLA-treated patients.

Lumbar- and drug reservoir puncture

Studies investigating the efficacy of EMLA in conjunction with lumbar- and drug reservoir puncture are summarized in Table 4.

Table 4 EMLA efficacy studies not submitted in all EU member states: Lumbar- and drug reservoir puncture

Investigator/ Report No.	Design	Number of patients EMLA/ Placebo	Age	Sex (boys/ girls)	Dose/ treatment time/ area of application	Summary of results
Trinquet 1995/ EM 9302	Multicentre, open	44/-	5 to 15 yrs	29/15	1-2 g/ 60 min/ area of puncture	Analgesic effect of EMLA was confirmed, and significant reduction in anxiety scores with use of EMLA prior to drug reservoir puncture, but not prior to lumbar puncture.

This was a rather small open study that will not be further commented.

Laser therapy

Studies investigating the efficacy of EMLA in reducing pain associated with laser therapy of dermal port wine stains (PWS's) in children are summarized in Table 5.

Table 5 EMLA efficacy studies not submitted in all EU member states: Laser therapy

Investigator/ Report No.	Design	Number of patients EMLA/ Placebo	Age	Sex (boys/ girls)	Dose/ treatment time/ area of application	Summary of results
Trinquet 1994 EM9301; Lemarchand Venencie et al. 1996	Double- blind, placebo- controlled, multicentre	23/23	>5 to <15 years (n=19) and adults (>15 years, n=27)	12/34	1.5-5g per 10 cm ² / 60-150 min/ 5-25 cm ²	Decrease in pain from laser treatment vs. placebo, after application of at least 60 min.
Katalinic 1988 802-10 AC068-1 (WG85EM01)	Double- blind, placebo controlled, cross-over	47/47	15 to 57 yrs	16/31	3 mL/ 60 min/ 2 cm line	EMLA mean pain level: 0.58 Placebo mean pain level: 4.1 Pain level significantly decreased for EMLA treated patients (VAS scoring, 0 to 100)
Tan 1987 3-EML-06	Double- blind, prospective, self- controlled	72/72	5 to 16 yrs	35/37	2.5g/ 60 min/ 1cm ²	EMLA reduced the patients mean pain score by 66% relative to placebo. Self-rating: EMLA significantly reduced pain. Ratings by patients, investigators and observers: EMLA significantly reduced pain scores.

Two of these studies were performed in both children and adults. In one study (Katalinic, 1988), only 3 children were included and in another study (Trinquet 1994), 17 children/adolescents were evaluable for efficacy.

Few children were included in two of the studies. Reduced pain scores were observed with EMLA compared with placebo. AEs were mainly blanching/pallor and slight, local skin reactions.

Curettage of molluscum contagiosum

Studies investigating the efficacy of EMLA in conjunction with curettage of molluscum contagiosum are summarised in Table 6.

Table 6 EMLA efficacy studies not submitted in all EU member states: Curettage of molluscum contagiosum

Investigator/ Report No.	Design	Number of patients EMLA/ Placebo	Age	Sex (boys/ girls)	Dose/ treatment time/ area of application	Summary of results
Oranje et al. 1990 802-10 AC082-1	Double-blind, placebo-controlled, parallel-group	58/25	4 to 12 yrs	42/41	1 g/ 15, 30, 60 min/ 2.5 x 2.5 cm	An application time of EMLA cream shorter than 60 min was satisfactory for the curettage of molluscum contagiosum in children
Rönnerfält et al. 1990 802-10 AC080-1 (86-EM14)	Open	29/-	4 to 9 yrs	9/20	1g/ 30 min/ 2.5 x 2.5 cm	EMLA applied for 30 min provided effective local anaesthesia for curettage of molluscs in patients with atopic dermatitis
Rosdahl et al. 1987 802-10 AC054-2	Open	55/-	3 to 14 yrs	14/41	1g/ 60min/ 2.5 x 2.5 cm	EMLA provided effective local anaesthesia for curettage of molluscs in children

Of three studies conducted in children prior to curettage of molluscum contagiosum, two were open and one was double-blind, randomised and placebo-controlled. In the latter study by Oranje et al (1990), different application times of EMLA were studied and no significant differences in pain ratings were observed between 15, 30 and 60 min application. There was a tendency to lower pain ratings with longer application times, though. The recommended application time for EMLA is generally 60 min before the needle insertion.

EMLA patch® and EMLA® cream therapeutic equivalence studies

Studies investigating the therapeutic equivalence of EMLA patch and EMLA cream are summarized in Table 7.

Table 7 EMLA efficacy studies not submitted in all EU member states: EMLA patch and EMLA cream therapeutic equivalence studies

Investigator/ Report No.	Design	Number of patients EMLA patch/ EMLA cream	Age	Sex (boys/ girls)	Dose/ treatment time/ area of application	Summary of results
Nilsson and Rotstein 1990a 802-10 AC093-1	Open, controlled, randomised, parallel group	31/32	5 to 15 yrs	36/27	One EMLA patch or 2.5 g cream/ 60-180 min/ dorsal side of the hand	The analgesic effect was similar with EMLA patch and cream
Stewart et al 1990 802-40 AC097	Open, comparative, multicentre, randomized, parallel group	96/100	3 to 10 yrs	100/96	One EMLA Patch or 2.5 g cream/ 60-180 min/ dorsal side of the hand	The analgesic effect was similar with EMLA patch and cream

The two studies were of open-label design, presumably due to problems with blinding due to different dosage forms, although this was not stated.

The overall conclusions on efficacy are that most of the submitted studies, both those included in the “Clinical overview 2006” and studies performed in other indications, were performed in the 1980s and the study reports were often brief and not up to current standards. Some studies were of double-blind, randomised, placebo-controlled design while others were open, uncontrolled. In several but not all studies, EMLA was found to reduce pain during various procedures. It is however, agreed that the results of the clinical studies submitted within this procedure do have any impact on the paediatric prescribing information provided in the current SmPCs for EMLA.

In one study, no significant differences in pain ratings were observed between 15, 30 and 60 min application time. The recommended application time for EMLA is 60 min before the needle insertion and there is no reason to change the currently proposed application time on the basis of this study.

Results for EMLA were also discussed by other MAHs, based on published studies or reviews. In some of these, efficacy could not be established for EMLA when used in circumcision procedures, venepuncture, etc. EMLA is not specifically indicated for use in circumcision procedures (see below). No modification of the indication was considered warranted on the basis of these data.

- Safety results

The MAH’s conclusion based on the previously submitted and the previously not submitted studies was that no new safety signals were observed in the additional studies not submitted to all EU member states, referred to in this document. Safety results from the studies are briefly mentioned above.

One specific aspect was mentioned, i.e. that both lidocaine and prilocaine are known to have concentration dependent growth-inhibitory effect on various bacteria and viruses. Therefore, live vaccines, which have to replicate in the body in order to work may be affected in case of inhibitory concentrations of the substances being present in the local tissue where the vaccine is injected. It is stated by the MAH that no significant difference in the proportion of children achieving a positive vaccine result have been found in clinical studies comparing EMLA with control groups. The MAH states that for those markets which have not yet included the current text on Warnings and precautions stated in CDS 2005, regarding the use of EMLA in conjunction with BCG vaccination, should revise their SmPC to include this precaution. No specific proposal is given by the MAH within this procedure, though.

PSUR data

PSURs for EMLA were submitted, covering the time period 01 April 2008 – 31 March 2009 as well as a PSUR Summary Bridging Report for the period 01 April 2004 – 31 March 2009 (dated 19 May 2009).

In the PSUR summary bridging report, exposure figures presented in the separate PSURs were summarized and the total worldwide exposure was estimated by AstraZeneca to be over 119 million patients (approximately 86 million patients for EMLA Cream and 34 million patients for EMLA Patch). Patient exposure was calculated from the amount of EMLA Cream and Patches delivered to wholesalers worldwide.

During the time period, 324 case reports met the criteria for inclusion in the PSURs, and these were associated with a total of 580 adverse events.

Regarding children, the MAH states that it may be noted that a relatively high proportion of adverse event reports with EMLA involve children. This is in accordance with the pattern seen previously, and most likely reflects the fact that EMLA is predominantly used in children. In the cumulative experience, methaemoglobinaemia has been reported more often in the lowest age groups. Apart from that, the types of symptoms reported in children are in general similar to those seen in adults, and there is no evidence of an increased risk of any ADRs in children.

The conclusion by the MAH in the PSUR Summary Bridging Report was that the present safety information in the Core Data Sheets, with some changes in some SmPC sections, accurately reflects the known safety profile for EMLA Cream and EMLA Patch. Revisions of the Posology and method of administration, Undesirable effects, Overdose, and Pharmacokinetic properties sections were proposed, to include a maximum recommended dose and area of application for adults in an outpatient setting, and to reflect the fact that in recent years methaemoglobinaemia has occasionally been reported also in adults after the use of EMLA Cream, not only in children.

The data submitted by the MAH do not give rise to any new safety concerns except those already known and labelled for EMLA cream and patch, i.e. transient local skin reactions at the application site such as paleness, erythema and oedema, and in rare cases methaemoglobinaemia in children and allergic reactions (e.g. anaphylaxis).

There are some published reports describing toxic effects associated with topical lidocaine use, such as EMLA, e.g. the following (see also below, discussion concerning Dynexan gel):

J Am Acad Dermatol. 2001 Feb;44(2 Suppl):399-400. Lidocaine and prilocaine toxicity in a patient receiving treatment for mollusca contagiosa. Touma S, Jackson JB.

A 3-year-old child with mollusca contagiosa whose caregiver applied a eutectic mixture of 5% lidocaine and prilocaine (EMLA) in excessive amounts developed adverse reactions, including methemoglobinemia and hypoxemia. Because of the significant systemic absorption of lidocaine and prilocaine, the patient required overnight admission to the pediatric intensive care unit for close monitoring.

Pediatr Dermatol. 2006 Nov-Dec;23(6):592-3. Methemoglobinemia and CNS toxicity after topical application of EMLA to a 4-year-old girl with molluscum contagiosum. Raso SM, Fernandez JB, Beobide EA, Landaluce AF.

Ned Tijdschr Geneesk. 2006 Aug 19;150(33):1805-7. [Coma in a child after treatment with the 'magic salve' lidocaine-prilocaine cream]. [Article in Dutch] Wieringa JW, Ketel AG, van Houten MA.

A 2-year-old girl lost consciousness after topical application of lidocaine-prilocaine cream (EMLA) in preparation for the removal of multiple mollusca contagiosa. Both the area on which cream was applied (80% of body surface) and the total amount of cream (90 g) exceeded the maximum dosage. Both methaemoglobinaemia and depression of the central nervous system occurred, resulting in loss of consciousness. The child was treated with 100% oxygen and fully recovered.

These cases mostly appear to have been related to use of excessive amounts of EMLA, not in accordance with the proposed labelling. However, the reports stress the fact that even if EMLA is a well-established product used for many years, the consequences of misuse can be serious.

However, the product information is adequate in this respect, e.g. concerning maximum amounts and duration of use.

The overall conclusion is that the results of the clinical studies submitted within this article 45 procedure do have any impact on the benefit/risk or paediatric prescribing information provided in the current SmPCs for EMLA.

Use of EMLA on genital mucous membranes and for male circumcision.

The MAH provided an extensive literature review and concludes that topical anaesthesia with EMLA Cream on genital mucous membranes and thin male genital skin in infants and young children is currently part of clinical practice. The recent CSP for EMLA cream does not contain any recommendations for use on genital mucosa in children, only in adults. Furthermore, in section 4.4 it is stated that “EMLA should not be applied to the genital mucosa of children owing to insufficient data on absorption of active substances. However, when used in neonates for circumcision, a dose of 1.0g EMLA on the prepuce has been proven to be safe.”

In comparison with the proposed paediatric doses for use on the skin, the doses for use on the genital mucosa are approximately half these doses in the lowest age groups (up to 12 months). In the older age groups, the maximum genital mucosa doses are only 20% and 15%, respectively, of the skin doses.

EMLA Cream is currently not approved for use on genital mucosa in children (below the age of 12 years) in any MS. The CSP for EMLA cream from the PSUR worksharing procedure of 2010 does not contain any recommendations for use on genital mucosa in children, and advises against such use in section 4.4. Therefore, the rapporteur for this paediatric procedure sees no reason to recommend the inclusion of such dosing recommendations for EMLA cream.

Due to inconsistencies in the SmPC texts for EMLA (AstraZeneca) in some member states, the issue of use of EMLA during male circumcision was further discussed in the procedure.

In the review “*Circumcision of neonates and children without appropriate anaesthesia is unacceptable practice*” by BR Paix and SE Peterson (Anaesth Intensive Care 2012;40:511-516), the authors conclude that EMLA gives insufficient anaesthesia for this surgical procedure. Their conclusion is based on the following studies:

TABLE 1
A comparison of the effectiveness of DPNB, Ringblock and EMLA cream for pain relief during routine neonatal circumcision

First author	Year	Number of subjects	Study design	Conclusion
Benini ⁴¹	1993	28	RCT of EMLA vs placebo	EMLA better than placebo but both groups clearly distressed
Taddio ⁴⁴	1997	59	RCT of EMLA vs placebo	EMLA better than placebo but did not eliminate pain
Lander ⁴⁷	1997	52	RCT of Ringblock vs DPNB vs EMLA vs placebo	Ringblock better than DPNB, DPNB better than EMLA, EMLA better than placebo, but with the EMLA group clearly distressed
Butler-O’Hara ⁴²	1998	64	RCT of DPNB vs EMLA vs placebo	DPNB better than EMLA, EMLA better than placebo
Howard ⁴⁸	1999	60	RCT of DPNB vs EMLA	DPNB better than EMLA
Brady-Fryer ⁴⁰	2004	35 trials	Cochrane systematic review of anaesthesia for RNC	DPNB substantially better than EMLA but neither fully eliminated circumcision pain

DPNB=dorsal penile nerve block, EMLA=eutectic mixture of local anaesthetic (lignocaine prilocaine cream), RCT=randomised controlled trial.

The introduction of this text (*However, when used in neonates for circumcision, a dose of 1.0 g EMLA has been proven to be safe.*) seems to be based on the Taddio study mentioned in the table above (published as: Taddio A, Stevens B et. al. Efficacy and safety of lidocaine-prilocaine cream for pain during circumcision. NEJM 1997;336:1197-1201.). In this trial, EMLA cream was only applied to the outer skin of the penis, no cream was applied on the inner genital mucosa. Statistically, there was a decrease in the recorded pain variables, compared with placebo, during the surgery.

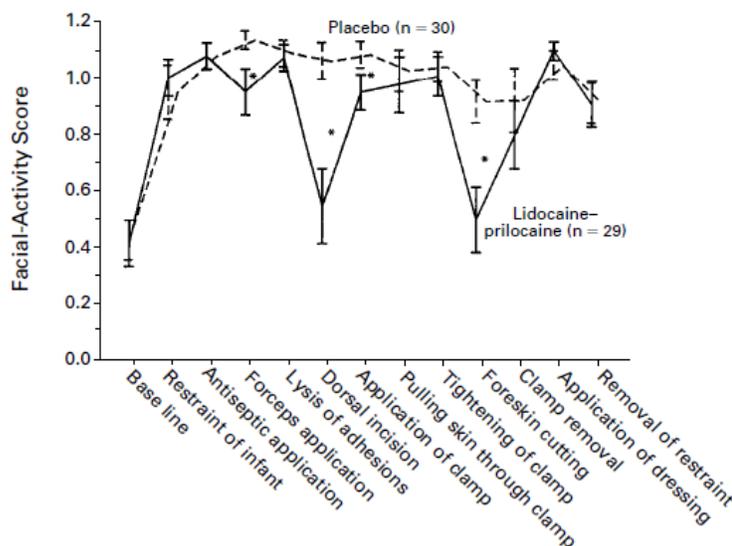


Figure 1. Mean Facial-Activity Scores during Circumcision in the Lidocaine-Prilocaine and Placebo Groups. A higher score indicates that the infant experienced more pain. The asterisks indicate a significant difference ($P < 0.001$) between the groups. $P = 0.01$ for the overall comparison between groups. Bars indicate 95 percent confidence intervals.

The safety variables were methemoglobinemia, lidocaine-prilocaine plasma concentrations, o-toluidine and clinical signs. None were considered to be clinically alarming.

From the authors' discussion:

We found that applying lidocaine-prilocaine cream to the penis reduced the pain of circumcision in neonates, as measured by facial activity, the duration of crying, and heart-rate changes. Although the use of lidocaine-prilocaine cream was associated with an overall decrease in pain, the magnitude of the effect varied during the procedure: it was less effective during phases associated with extensive tissue damage such as lysis of adhesions and tightening of the clamp. The neonates in the lidocaine-prilocaine group still had pain during the circumcision, albeit at an attenuated level. The efficacy of lidocaine-prilocaine cream is affected by the method of application and the dosage. Uneven distribution of cream may cause variations in the tissue concentrations of lidocaine and prilocaine and subtherapeutic anesthetic concentrations in some regions.

After reviewing the publications in table 1, the Rapporteur agrees with the authors (Paix & Peterson) that even if EMLA cream reduces pain in a statistically significant way, the reported reduction seems insufficient to be ethically acceptable. Therefore, including information on the

use of EMLA in circumcision procedures in the EMLA national SmPCs cannot be recommended. Even if the statement in section 4.4 of the CSP only refers to *safety* of EMLA for use in neonates for circumcision, proof for sufficient *efficacy* seem to be lacking, and thus, any mentioning of use of this product for circumcision procedures should be removed to avoid this type of use. If circumcision is medically motivated, there are fully functional anaesthetic techniques available.

Jelliproct (Grünenthal)

Grünenthal is the MAH for Jelliproct ointment and suppositories, registered in Germany under the following tradenames:

Jelliproct Salbe (ointment) Reg. Nr. 789.00.00 Reg. date: 30 November 1979

Jelliproct Zäpfchen (suppositories) Reg. Nr. 789.00.01 Reg. date: 30 November 1979

Jelliproct ointment contains 0,25 mg fluocinonide and 50,0 mg lidocaine hydrochloride per 1 g and Jelliproct suppositories contain 0,25 mg fluocinonide and 60,0 mg lidocaine per 1 suppository. The indications approved since August 2008 are as follows:

Jelliproct ointment:

For short-term symptomatic treatment of inflammatory diseases in the area of the anus, especially haemorrhoids, proctitis and anal eczema. Application in connection with proctological interference.

Jelliproct suppositories:

For short-term symptomatic treatment of inflammatory diseases in the area of the rectum, especially haemorrhoids and proctitis. Application in connection with proctological interference.

A specific paediatric posology or a lower age limit were not included. Twice daily application is recommended for both ointment and suppositories and a duration of 1-2 weeks use should not be exceeded.

No changes in the currently approved SmPC were proposed.

The MAH submitted one multicentre, post-marketing, prospective, observational, non-interventional study (NIS) with the objective to investigate the efficacy, tolerability and safety of Jelliproct in the therapy of inflammatory diseases of the perianal region. No pharmacokinetic or pharmacodynamic studies were presented in paediatric patients.

Multicentre postmarketing, non-interventional clinical trial for the treatment of inflammatory skin diseases of the peri-anal region

The study was performed in 2001 and 2035 patients in the age range 2 to 94 years were treated with Jelliproct ointment and/or Jelliproct suppositories according to the at that time approved SmPC. Only 3 children (2-11 years) and 12 adolescents (12-18 years) were included in the study. No infants were included. The presentation of the results in the clinical overview mainly focused on safety findings and the findings are summarized in the following tables.

Table 1: Line listing – Patient group: children (N=3)

Patient number	Age (Years)	Diagnosis	Application form	Application frequency (Days)	Duration (Days)	AE	Tolerance (assessment by doctor)
944	2	Proctitis	Ointment	2	11	None	Very good
942	8	Anal eczema	Ointment	2	7	None	Very good
1942	10	Anal fissure	Suppository	2	8	None	Very good

Table 2: Line listing – Patient group: adolescents (N=12)

Patient number	Age (Years)	Diagnosis	Application form	Application frequency (Days)	Duration (Days)	AE	Tolerance (assessment by doctor)
425	13	Anal eczema	Ointment	2	15	None	Very good
383	14	Anal eczema	Ointment	2	17	None	Very good
20	15	Anal eczema	Ointment	2	13	None	Very good
1097	16	Anal eczema	Ointment	1	15	None	Very good
324	17	Haemorrhoidal disease (1st grade)	Ointment	2	9	None	Very good
1335	17	Haemorrhoidal disease (1st grade)	Ointment	2	14	None	Very good
1591	17	Anal fissure	Ointment	2	17	None	Good
251	18	Anal eczema	Ointment	2	11	None	Very good
312	18	Proctitis	Suppository	2	11	None	Very good
644	18	Psoriasis	Ointment	2	11	None	Good
921	18	Anal fissure	Ointment and suppository	2	51	None	Very good
1329	18	Anal eczema	Ointment	2	16	None	Good

Most patients were treated with the ointment formulation. The duration of treatment was in the range 7-17 days in most patients except in one psoriasis patient who was treated more than 51 days. No AEs were reported in the paediatric patients and the tolerability was rated as “very good” or “good”.

The NIS study included on 15 children and adolescents, and thus, provides limited information on the use of Jelliproct ointment and suppositories in the paediatric population. In this limited group, no AEs were reported and the tolerability was rated good or very good. The duration of treatment was approximately 1-2 weeks in most patients, i.e. in accordance with the approved labelling. The applicant’s conclusion is that the efficacy/risk-ratio is considered positive for children and adolescents according to the data of the NIS. The number of patients in the paediatric population is too small to draw conclusions from, however, the data give no cause for concern in terms of safety.

PSUR data

During the post-marketing period of Jelliproct ointment and suppositories, no evidence of adverse events has been reported with respect to the treatment of paediatric groups. The MAH refers to the latest submitted PSUR (4,5 years, DLP 30 May 2004). The next PSUR had DLP 30 May 2009. The PSURs contained no information of concern for the paediatric population.

Overall conclusion

The MAH Grünentahl considers that no changes to the currently approved SmPCs are warranted. The current SmPC wording regarding the paediatric population is not in agreement with the Guideline on Summary of Product Characteristics (September 2009) and should therefore be updated with information on age groups in section 4.1:

X is indicated in <adults><neonates><infants><children> <adolescents> <aged x to y <years, months>>.

Dynexan (Kreussler Pharma)

Kreussler Pharma is the MAH for a medicinal product presented as a gel containing 2 % lidocaine hydrochloride as active pharmaceutical ingredient, Dynexan 2 %, gingival gel/paste. The medicinal product is distributed in several European countries under different names. The longest history exists in Germany where the medicinal product was registered first in 1976. In a renewal procedure in 2005, the indication and posology sections were amended to read as follows:

Indication: “For temporary symptomatic treatment of pains at the oral mucosa, gingiva, and lips”.

Posology: “Adults: 4-8 times daily a pea-sized amount Dynexan Mundgel (this corresponds of about 0.2 g gel or 4 mg lidocaine respectively). A total dosage of 40 mg lidocaine should not be exceeded.

For children and infants dosage has to be done individually considering age and body weight (max. 4 times daily a pea-sized amount).”

In France, the marketing authorization for Dynexan 2 % was granted in 1999, initially for use of the medicinal product in adults only. Subsequently, a clinical phase III study was performed to demonstrate efficacy and safety of the product in children. Based on these study results, Kreussler applied for extension of the indication and in December 2002 the AFSSAPS granted the use of the medicinal product for children with an age from 6 years on. In France, the indication and posology sections read as follows:

Indication: “Symptomatic short-term treatment of painful lesions in the oral cavity.

Local contact anaesthesia prior to instrumental examinations in odontology / stomatology.”

Posology: “Adults: Application of 0.5 g cream, max. four times daily, corresponding to 40 mg lidocaine.

Children from 6 to 15 years: Application of 0.5 g cream, max. four times daily, corresponding to 40 mg lidocaine.”

The product is not approved in other MS. No changes in the currently approved SmPCs were proposed.

The MAH Kreussler Pharma submitted reports for a Comparative Clinical Trial Investigating Dynexan 2% Gingival Paste, against Placebo in Children and A randomised, double blind,

parallel group, 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 (KRE 001/00). In addition four published studies were submitted. No pharmacokinetic or pharmacodynamics studies were presented in paediatric patients.

3. Clinical studies

Comparative Clinical Trial Investigating Dynexan 2% Gingival Paste, against Placebo in Children

➤ **Methods**

This study was performed with the objective to produce data to extend the indications for Dynexan 2% to children of more than 6 years of age, by demonstrating its efficacy in the short-term relief from pain in the buccal cavity associated with mucosal lesions or prevention of pain that may develop during prosthetic or surgical procedures. The study had 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 or requiring local anaesthesia as prevention of pain caused by dental or surgical procedures were included. The planned number of subjects was 60 children.

The treatments were Dynexan 2% 0,5 g, gel containing 10 mg lidocaine hydrochloride and placebo gel. The gel was applied on the mucosa by massage for one minute. Excess gel was then removed.

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 of allergic or local reactions in the region of application of the trial product and difference in pain intensity before and after treatment as assessed by the dentist, using the scale "absent, minor, moderate or strong pain".

➤ **Results**

64 subjects (33 placebo and 31 Dynexan) were randomised and included in the safety population. Two subjects (one placebo and one Dynexan) were unable to perform the VAS assessment, and were excluded from the efficacy data set.

Baseline characteristics (age, sex, weight, height, history of buccal/dental interventions) were comparable in the two groups. Mean age was 10 ± 2 years in both groups. The indication for local anaesthesia was comparable in the two groups, with the main indication being placement of dental clamps (Dynexan group, 58.1%, Placebo group 63,6% NS) followed by buccal wounds (Dynexan group, 19,4%, Placebo group 24.2% NS) and aftae. Pre-treatment pain intensity levels were comparable in the two groups (Dynexan group 37.2 ± 20.2 and Placebo group 34.8 ± 23.9 ; NS) as assessed by the child using VAS. The percentage of children described by the Investigator as anxious or frightened at baseline was greater in the Dynexan group, but this was not statistically significant.

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 then measured three minutes after the end of gel application (T2). In the buccal/dental intervention group pre-treatment pain intensity was assessed before treatment but 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 was assessed (T2).

There was a statistically significant ($p < 0.05$) difference in pain intensity reduction (from T0 / T1 to T2) 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.

This study had an adequate design and an effect in pain intensity reduction vs. placebo was shown. Children were included in a range from 6 to 15 years of age with a considerable number of children aged between 6 and 8 years (mean age 10 years).

KRE 001/00. A randomised, double blind, parallel group, 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.

➤ **Methods**

The objective of this study was to find and test assessment criteria from the different behaviours and reactions of children with pain perception and to show in a future main study that Dynexan®A gel is also effective and well tolerated in infants with teething trouble. It was investigated whether efficient relief of teething pain is achieved and the product is well tolerated.

The study was a randomised, double-blind, parallel group, comparative, placebo controlled phase IV study. Infants 6 to 12 months of age with pain in the region of the tooth with visible tooth tips and/ or visibly discoloured, bleeding gingival, were included. The planned sample size was 20 subjects. The treatments were Dynexan® A Gel (lidocaine hydrochloride) or gel without an active ingredient. A pea-sized amount of gel was applied onto the finger tip and rubbed on to the gingiva, for a maximum of 4 times daily for a total of 8 applications or 5 days. The outcomes/endpoints were: assessment of efficacy and tolerability by the parents and by the investigator; assessment of symptoms of teething trouble by the parents and by the investigator and nature and severity of adverse events. This was a hypothesis-generating study, and hence, only descriptive statistical methods were used and no sample size calculations were made.

➤ **Results**

A total of 25 patients were included in the study. Ten patients did not use the trial medications and 15 patients completed the study with a second visit. Only the data of the 13 patients who completed the study per protocol and for whom at least one protocol entry was available (parents questionnaire) could be considered for the descriptive efficacy analysis. Data on safety/tolerability were recorded for all evaluable patients. Twelve of the 25 patients included were female, 13 were male. The mean age was 8.8 months and the mean weight was 8.6 kg.

It was concluded by the sponsor that the study provided some information which would allow a rational planning of the design of a placebo-controlled main study to be made, but 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 results, the patients showed mainly typical symptoms commonly occurring concomitantly with teething trouble: vomiting, diarrhoea or retching.

This was a very small study of mainly explorative character and is, thus, not considered to contribute to the assessment of this product.

The overall conclusions on efficacy were that the study called “Comparative Clinical Trial Investigating Dynexan 2% Gingival Paste, against Placebo in Children” could provide some support for efficacy of Dynexan gel in children with pain and mucosal lesions of the buccal cavity. Study KRE 001/00 performed in a small number of babies aged 6-12 months does not contribute to the assessment of this product.

- Safety

Information from post-marketing experience in Germany

In the study “Comparative Clinical Trial Investigating Dynexan 2% Gingival Paste, against Placebo in Children”, no local or general reactions were reported in any of the treatment groups. In the second study in younger children, the patients showed mainly typical symptoms commonly occurring concomitantly with teething trouble: vomiting, diarrhoea or retching. The study was very small and the AEs were not clearly presented.

An investigation was performed on the safety of medicinal products used in children younger than 12 years. The reporting period was from 2005 to 2007. In this time about 2.7 million tubes of Dynexan were sold. Because of prescription-data it was known that at least 320,000 children younger than 12 years used the medicinal product during the reporting time. It was also deemed likely that significantly more children used the drug on the basis of a recommendation in addition. Ten adverse reactions were reported (all in adults),

A PSUR written by Kreussler France and dated January 2007 was attached. The PSUR covered the period 2006-01-01 to 2006-12-31 and the estimated total patient exposure was 1 282 000. Only one suspected ADR was reported, listed as serious, and this was an allergic reaction (swollen face and tongue) in a 90-year old female.

No obvious safety concerns were identified in the two studies, with a relatively small number of children, or in the safety investigation based on prescription-data or the submitted PSUR.

Concerning the overall conclusions on safety, published information is available concerning lidocaine use in small children and possible toxicity. In an article by Curtis LA et al., (J Emerg Med. 2009 Jul;37(1):32-9. Are one or two dangerous? Lidocaine and topical anesthetic exposures in children.), cases of toxicity and deaths associated with topical local anaesthetic use are reviewed. Topical use of lidocaine can be associated with safety problems, particularly in small children, infants, babies and neonates who are expected to be more sensitive to adverse events, e.g. CNS toxicity. Also, the use of lidocaine on mucous membranes is expected to be associated with a risk of higher systemic absorption compared with administration on intact skin.

During the procedure, the MAH was asked to justify the indications for Dynexan gel and the use in children below the age of 6 years. It was concluded that there is no pivotal clinical trial available to support the use of Dynexan 2 % in small children but the MAH refers to well established use of the product. This is partly based on sales and prescription figures since the product is only allowed to be prescribed for children younger than 12 years of age but not for adults in Germany.

A PSUR with DLP 31 December 2009 was also submitted. This PSUR describes 21 spontaneous reports about adverse drug reactions in connection with Dynexan[®] Mundgel and 5 literature case reports concerning comparable products. There was no increased reporting frequency of any adverse drug reaction and no changes in the characteristics of the reported adverse drug reactions occurred (e.g. related to children). Very few of both the spontaneous reports and literature reports concerned use in children. The benefit-risk assessment of Dynexan[®] Mundgel was deemed as positive and no safety actions of any kind were necessary at present.

Overall conclusion

Dynexan gel is only approved and marketed in two MS, Germany and France, with somewhat different indications and age limits for use. In comments received by Germany, it is stated that the clinical usage of Dynexan is well established in children below the age of 6 years and there are no established safety concerns of note, for instance based on the latest PSUR.

It may not be relevant to limit the use only to an older age group in Germany for a product that has been on the market for many years with no obvious safety concerns. On the other hand, it may not be appropriate to suggest that the age limit of 6 years applied in France should be removed. This would likely necessitate submission of a type II variation for a change in the posology section of the SmPC in France.

Regarding other MS that do not have the product approved, the indications approved in DE and FR may not be considered appropriate, e.g. to use a lidocaine-containing product for treatment of conditions like teething pain.

The following SmPC modifications are proposed:

Section 4.1

It should be stated in which age groups the product is indicated, specifying the age limits, e.g. ***X is indicated in <adults><neonates><infants><children> <adolescents> <aged x to y <years, months>>.***

Published studies submitted by Kreussler

Several publications were also included, e.g. with EMLA for intra-oral use in dentistry procedures, EMLA used as an aid to suture removal following cleft lip repair, a comparative study of EMLA, a lidocaine 5% ointment and benzocaine 18 % gel, another comparative study of EMLA, Xylocaine 10 % (aerosol containing 10 % lidocaine) and two other local anaesthetics for use in intra-oral injection pain in 10-15 years-old children. Further studies also evaluated EMLA for use in paediatric dentistry, EMLA for use as a topical anaesthetic in sealant placement with rubber dam and topical lidocaine (as a spray) used in dental extraction. Yet another study evaluated the effectiveness of a lidocaine and benzyl alcohol solution in the relief of the pain and discomfort of infant teething.

The studies referred to were not performed with Dynexan 2% gel but with other lidocaine containing products, e.g. EMLA. Most of these studies involved use of EMLA or other lidocaine-containing products for use in dentistry procedures or infant teething. This is not an approved indication for EMLA and the studies were not reviewed in further detail and are not considered to warrant any changes in the proposed indications for EMLA.

Cathejell Lidocaine (Montavit)

The product is a combination of lidocaine hydrochloride (20 mg/g) and chlorhexidine dihydrochloride (0.5 mg/g) available as a gel for intra-urethral instillation.

The product is used for reduction of pain during catheterization and prevention of onset of urinary tract infections following transurethral procedures. However, the indication and the dose recommendation for children were not described.

No changes in the currently approved SmPC for Cathejell Lidocaine are proposed.

The MAH submitted 37 published studies together with an Overview. The studies considered relevant are described below. No paediatric pharmacokinetic or paediatric pharmacodynamic with the combination product were performed by the MAH. A Post Marketing Surveillance study, which was aimed at evaluation of efficacy and safety under routine therapeutic conditions, was submitted.

Pharmacokinetics in children

Summary of pharmacokinetic studies

Study Reference	Study Objective	Study Design	Treatments	Subjects No. (M/F) Type Age in years: mean (range)
<i>Lidocaine</i>				
Weatherstone et al., 1993	Safety (systemic lidocaine absorption) and efficacy	Randomized, double-blind, placebo-controlled	Topical 30% lidocaine cream or the cream base	30 (30/-) Newborns undergoing circumcision 6-72 hours old
Read and Bach, 1980	Determination of serum and urinary concentrations	Open-label	2% lidocaine hydrochloride gel applied over wounds	13 (10/3) Patients with plastic surgery procedures incl. burns (8-70)
<i>Chlorhexidine</i>				
Thomas et al., 1969	Determination of plasma concentrations	Open-label	Topical lidocaine spray, 400 – 1000 mg (10 mg/spray)	22 (-/22) Women in labour (17-34)
Cowen, 1979	Absorption of chlorhexidine from the skin	Open-label	4% chlorhexidine gluconate bath	34 (18/16) Newborns

Results:

Study Reference	Main outcome
Weatherstone et al	<u>Lidocaine</u> : Serum lidocaine content was determined approximately 15 minutes after circumcision in 14 subjects treated with the lidocaine cream. The plasma levels were $0.27 \pm 0.19 \mu\text{g/ml}$ (range 0.1-0.7 $\mu\text{g/ml}$). No adverse side effects were observed.
Read and Bach	<u>Lidocaine</u> : A marked degree of absorption occurred in the two patients with thermal burn probably depending on the large surface area of the wound.
Thomas et al	<u>Lidocaine</u> : Following topical application of lidocaine as an aerosol to the vagina, perineal skin or for episiotomy repair in women in labour resulted in the plasma levels below 1 $\mu\text{g/ml}$ independent of the dose used or type of skin or membrane sprayed.
Cowen et al	Only chlorhexidine absorption was assessed.

The results from the submitted studies show that lidocaine levels after a single administration were in the range of 0.1-0.7 $\mu\text{g/ml}$ in newborn babies undergoing circumcision which are well below the “toxic” level. However, no data from repeated dosing of lidocaine is available. The open-label studies are all too small and no real conclusions can be drawn. The data referred to come from a range of different products but there are no PK studies for the combination product, which is considered a deficiency.

Clinical efficacy

Efficacy studies in children

Study Reference	Primary Endpoint(s)	Study Design	Treatments	Subjects No. (M/F) Type Mean age in years (range)	Main outcome
Gerard et al., 2003	Assessment of procedural pain and distress by Oucher pain scale and 7-point Likert-type scale, respectively	Prospective, double-blind, randomized, placebo-controlled	Lidocaine gel 1.5-6 ml Chlorhexidine gel (as placebo)	20 (4/16) Children undergoing catheterization for cystoscopy 7.7 (4-11) Lidocaine: 91.9±23.8 months Placebo: 93±24.9 months	Lidocaine vs control Self-rated pain: 21±19.69 vs 65.5±26.29 (p=0.001) Distress: 2.65±1.97 vs 4.7±2.07 (p=0.007)
Kozer et al., 2006	Assessment of procedural pain by DAN neonatal acute pain scale	Prospective, single-blind, randomized (to SPA or TUC), controlled	2% lidocaine hydrochloride gel	58 Infants undergoing SPA or TUC SPA: (17/10) TUC: (14/10) (0-2 months) SPA: 27.7±14.8 days TUC: 36.5±12.3 days	Mean±SD DAN: 7.0±1.9 (SPA) 4.5±2.1 (TUC) Mean±SD VAS by parent: 63±27 (SPA) 46±26 (TUC) Mean±SD VAS by nurses: 63±18 (SPA) 43±25 (TUC)

Study Reference	Primary Endpoint(s)	Study Design	Treatments	Subjects No. (M/F) Type Mean age in years (range)	Main outcome
Vaughan et al., 2005	Assessment of procedural pain by FLACC	Prospective, double-blind, randomized, placebo-controlled	2% lidocaine gel Conventional nonanesthetic lubricant	115 Infants undergoing BC Lidocaine: 203 days; 56 patients, 49% F Control group: 259.6 days; 59 patients, 50% F	Lidocaine vs control Mean±SD (95% CI) FLACC during BC: 7.37±2.87 (6.62 to 8.12) vs 7.55±2.56 (6.87 to 8.24) (p=0.96) FLACC after procedure: 2.03±2.03 (1.5 to 2.56) vs 2.59±2.14 (2.02 to 3.16) (p=0.11)
Scholtmeijer and Dzoljic-Danilovic, 1990	Assessment of disinfecting effect	Uncontrolled	Lubricant containing 2% lidocaine HCl, 0.025% propyl-p-hydroxybenzoate, 0.06% methyl-p-hydroxybenzoate and 0.05% chlorhexidindigluconate	100 (55/45) Children undergoing cystoscopy	Under therapy urethral smear became: Sterile: 61.5% Substantial reduction: 26.5%
Panosch et al., 2008	Assesment of procedural pain according to a 10-dimensional scale	Post-Marketing Surveillance	11.9 g Cathejell Lidocaine (3.125-37.5)	73 (14/58; 1 missing) Patients undergoing catheterization, cystoscopy, TUMT 41.3 (0.14-17.71)	Mean experienced pain: Infants: 1.8 Children: 1.438 Adolescents: 1.167
Study Reference	Primary Endpoint(s)	Study Design	Treatments	Subjects No. (M/F) Type Mean age in years (range)	Main outcome
Bhananker et al., 2006	Assesment of post-operative pain by mCHEOPS	Prospective, double-blind, randomized, controlled	0.5 ml 2% lidocaine topical Acetaminophen 30 mg/kg p.o.	124 Children undergoing bilateral myringotomy and tube placement Lidocaine: 72 (48/24) 4.6±2.3 Acetaminophen: 52 (35/17) 4.6±2.1	Median (range) scores in the DCSU at 15 and 30 min were similar, i.e., 5 (4-9) in the acetaminophen group and 4 (4-8) in the lidocaine group.
Adults and adolescents					
Pearman et al., 1991	Assessment of incidence of significant bacteriuria.	Prospective, open, randomized, controlled	Group A: Nelaton catheter plus the instillation of 50 ml Trisdine Group B: O'Neil catheter (prelubricated, polyvinyl chloride Nelaton catheter with a special introducer)	43 (36/7) Patients with acute spinal cord trauma A 19 males: 29 (17-52) A 1 female: 46 (22-70) B 17 males: 22 (13-41) B 6 females: 33 (20-45)	No individual results on adolescents presented.
El-Sherif and Prasad, 1995	Assessment of local anesthetic effect	Uncontrolled	2% lidocaine gel	34 (34/0) Patients with urethral stones 38.7±10.5 (7-55)	No individual results on children presented.

Study Reference	Primary Endpoint(s)	Study Design	Treatments	Subjects No. (M/F) Type Mean age in years (range)	Main outcome
Birch et al., 1994	Assessment of procedural pain by VAS (patient) and 4-point scale (physician)	Prospective, double-blind, randomized, placebo-controlled	10 ml 2% lidocaine gel 10 ml of plain aqueous gel [10-15 min]	138 (138/-) Patients undergoing flexible cystoscopy Lidocaine: 75 (75/-) 67.7±12.54 (17-88) Plain gel: 63 (63/-) 67.8±13.06 (21-90)	No individual results on adolescents presented.

Kozer et al: DAN (Douleur Aigue du Nouveaune), SPA (suprapubic aspiration), TUC (transurethral catheterization)

Vaughan et al: BC (urinary bladder catheterization)

Panosch et al: *Age distribution:* Infants (1 -24 months): 13 patients; children (2-11 years): 63 patients; adolescents (12-16/18 years): 7 patients; adults 130 patients. *Gender distribution (M/F):* Infants: 5/7; children: 6/47; adolescents: 3/4 adults 76/54 patients. TUMT (Transurethral Microwave Thermotherapy).

Topical use of local anesthetics in neonates

C.M. Essink-Tjebbes, Y.A. Hekster, K.D. Liem and R.T.M. van Dongen, Pharm World Sci, 1999 Aug; 21 (4): 173-176

Introduction: Various local anesthetics as in lidocaine ointment, amethocaine cream and EMLA® cream are used topically for minor invasive interventions, such as venipuncture, both in children and adults. Since neonates have a nervous system that, albeit immature, enables them to feel pain, analgesia for these procedures is also indicated. Several studies in neonates have been carried out to establish effectiveness and safety of topically applied local anesthetics. These studies are reviewed in order to assess effectiveness and safety.

Methods: A Medline search was made in order to review all studies on effectiveness and safety of topical use of local anesthetics in neonates. Effectivity or safety studies using local anesthetics for circumcision were rejected.

Results: Seven studies on effectiveness were found: Three studies examined lidocaine ointment and four examined EMLA® cream. Effectiveness of lidocaine ointment was questionable in two studies and negative in one. Effectiveness of EMLA® cream was positive in two studies and negative in the other two. Four studies were found on safety of EMLA® cream. All studies indicated that use of EMLA® cream was safe.

Discussion: The poor effectiveness found in the reviewed studies is possibly due to too long an application time, a lipophilic carrier used and difficulties in assessing pain. The time of application is often based upon studies in children. Since the skin of neonates acts more as a mucosa than as mature skin the local anesthetics are able to cross this barrier more rapidly. Also a high bloodflow in the heel enhances the uptake of the drug. The application time in neonates should therefore be reduced compared to children. The use of a lipophilic carrier should be avoided since a lipophilic carrier impedes the local anesthetic to be absorbed, leading to reduced effect. Various methods of pain assessment were being used. Since not all methods used are validated it is difficult to obtain an objective end point.

Conclusion and recommendation: The articles reviewed are non conclusive in their results of effective analgesia. Due to a lipophilic base form and a hydrophilic matrix EMLA® cream is most effective. An application time of 30 minutes is recommended. In spite of the present precautions due to fear of methemoglobinemia, use of EMLA® cream proved to be safe when used once a

day. Since the clinical situation often requires more than one application a day, more research is needed to establish a safe and effective local anesthetic which can be applied topically several times a day in the neonate.

The MAH submitted published paediatric data covering both active substances. For the lidocaine/chlorhexidine combination there are clinical data from one post marketing surveillance study (Panosch et al; Cathejell Lidocaine product) and one uncontrolled study (Scholtmeijer and Dzolijic-Danilovic; Instillagel product). Cathejell Lidocaine contains chlorhexidine hydrochloride whereas Instillagel contains chlorhexidine gluconate, besides lidocaine. The two products can be considered to be comparable.

The efficacy and safety of Cathejell Lidocaine was evaluated in a Post Marketing Surveillance study under routine therapeutic conditions. The study (Total N= 203) included 13 Infants (1 -24 months), 63 children (2-11 years), 7 adolescents (12-16/18 years) and 130 adult patients. The primary efficacy parameter was the perceptions of pain during catheterization procedure and the results indicated that there was no statistical significant difference between the perception of pain between the age classes.

In a small study in children (N=20) undergoing urethral catheterization lidocaine was statistically significantly better in reducing pain and distress when compared to the placebo chlorhexidine (Gerard et al). However, the study consisted of a limited number of children and the selection of chlorhexidine as a placebo control can be questioned. In a study in infants (N=115) there was no difference between lidocaine and control treated groups with respect to experienced pain during catheterization (Vaughan et al). In conclusion, there are only limited clinical data supporting the reduction of pain effect of lidocaine/chlorhexidine during catheterization.

The disinfecting effect of lidocaine/chlorhexidine gel (Instillagel) was studied in 100 children undergoing cystoscopy by Scholtmeijer and Dzolijic-Danilovic. Bacterial test were performed immediately before and after the procedure. The data showed that after treatment urethral smears became sterile in 61.5% of the 75 children presenting a positive urethral culture. Further, a substantial reduction is observed in another 26.5%. Thus, the data indicate a disinfecting effect, which is considered to relate to the chlorhexidine component.

The topical use of lidocaine and EMLA in neonates was reviewed by Essink-Tjebbes et al. An application time of 30 minutes is recommended by the authors who further consider that more research is needed to establish a safe and effective local anesthetic which can be applied topically several times a day in the neonate. However, the recommended application time for EMLA cream and patch is generally one hour, which is considered adequate (see also AstraZeneca; EMLA).

Overall, on the basis of the submitted data the clinical effect of reducing of pain when used during catheterization is limited for infants and children. Even if the results are not very impressive, the data do not give any reason to change the current recommendations regarding the use of this product in children and adolescents.

Clinical safety

Post marketing experience

According to the MAH, the PSUR between 1, January 2000 to October 25, 2006 confirms the well established safety profile of lidocaine and chlorhexidine. No PSUR was submitted.

The MAH has in response to the raised question submitted a PSUR addendum report covering the period 3 December 2009 to 14 March 2011.

During the reviewed period, one report on 3 non-serious adverse reactions became available and no information has been identified as potential safety issue in estimated 5,007,809 patients exposed to Cathejell with Lidocaine. The safety data presented are in accordance with previous knowledge (2 case reports in estimated 15,721,057 patients in the recent 3-yearly PSUR (2 December 2006 to 02 December 2009)) and the reference safety information.

Thus, the product has a well established safety profile and there is no new safety concern. Thus, there is no need to update the SmPC based on the submitted new safety data.

Overall conclusion

The indications for the Cathejell with lidocaine vary across the countries where the product is approved. In all countries it is used as a local anesthetic of urethra and lubrication of urinary bladder in catheterisation, cystoscopy and other intraurethral manipulations. In most of the countries it is also claimed to have a disinfectant action. In some MS an additional indication is claimed i.e. for mucosal anaesthesia and as a lubricant for tracheal intubation.

The dose recommendations for use as a local anesthetic of urethra and lubrication of urinary bladder in catheterisation, cystoscopy and other intraurethral manipulations seem in general harmonized for adults (presumably men). The most common dose recommendation is:

“Adult men: the syringes contain 12.5 g or 8.5 g gel of which approx. 10 g or 6 g are instilled into the urethra. The size of syringe used depends on the individual anatomical conditions of the urethra. The contents of one syringe are sufficient to fill the urethra; not more than one syringe should be instilled. The effect starts after 5-10 minutes and lasts for 20 – 30 minutes.

In **women, children (2-12 years) and adolescents (under 18 years)** the effect of Cathejell with lidocaine is not so well demonstrated and therefore the need to use it should be assessed by the doctor. Specific dosage recommendations cannot be given for these groups of patients, but as a general rule, the amount of gel instilled is adapted to the individual anatomical conditions of the urethra.

The systemic absorption of lidocaine can be increased in children and caution is accordingly required. In general, the maximum dose in children aged 2 to 12 years of 2.9 mg/kg lidocaine hydrochloride should not be exceeded.

Cathejell with lidocaine must not be used in **children under 2 years** (see section 4.3).”

Some of the SmPC have only a short description regarding dose recommendation, e.g. “ the syringes contain 12.5 g or 8.5 g gel of which approx. 10 g or 6 g are instilled into the urethra.”

Even though no changes in the currently approved SmPC for Cathejell Lidocaine are proposed by the MAH, an inclusion of a comment regarding the use in women, children (2-12 years) and adolescents and in children under 2 years, as described above, could be considered.

Overall, the clinical effect of reducing pain during catheterization in infants and children seems weak on the basis of the submitted studies. There are some data indicating a disinfecting effect of a lidocaine/chlorhexidine combination. It should be noted that Cathejell Lidocaine is not approved in Sweden (Rapporteur) and we don't have access to the data in the MAA file. Even if the results are not very impressive, the data do not give any reason to change the current recommendations in the countries where the product is approved regarding the use of this

product in children and adolescents. The product has a well established safety profile and there is no new safety concern.

The following SPC modifications are proposed:

The Rapporteur is aware of that the MAH already has submitted national variation applications to a number of the concerned member states and therefore the proposed modifications could already have been considered.

The following SPC modifications are proposed:

Section 4.1

It should be stated in which age groups the product is indicated, specifying the age limits, e.g. ***X is indicated in <adults><neonates><infants><children> <adolescents> <aged x to y <years, months>>.***

Section 4.2

The following should be included:

“In women, children (2-12 years) and adolescents (under 18 years) the effect of Cathejell with lidocaine is not so well demonstrated and therefore the need to use it should be assessed by the doctor. Specific dosage recommendations cannot be given for these groups of patients, but as a general rule, the amount of gel instilled is adapted to the individual anatomical conditions of the urethra. The systemic absorption of lidocaine can be increased in children and caution is accordingly required. In general, the maximum dose in children aged 2 to 12 years of 2.9 mg/kg lidocaine hydrochloride should not be exceeded.

Cathejell with lidocaine must not be used in children under 2 years (see section 4.3).”

Section 4.3

Relevant text should be included regarding children.

Orofar (Novartis)

The product is a combination of benzoxonium chloride and lidocaine hydrochloride, available as lozenges, gelsollets (both containing 1mg benzoxonium and 1 mg lidocaine), oromucosal spray (containing 2 mg benzoxonium and 1.5 mg lidocaine per ml) and oromucosal solution (containing 0.5 mg benzoxonium and 0.5 mg lidocaine per ml).

The combination product is indicated for treatment of infections in the mouth and throat:

- sore throat associated with colds, pharyngitis or laryngitis
- stomatitis, aphthous ulcers, gingivitis
- adjuvant in tonsillitis

The oral solution is also recommended for the treatment of dental plaque.

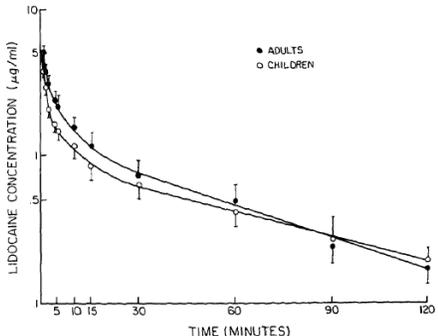
The product is recommended for adults and for children and adolescents aged 4 years and above.

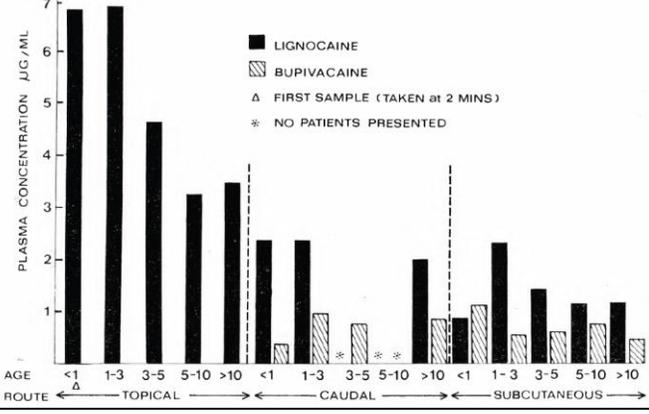
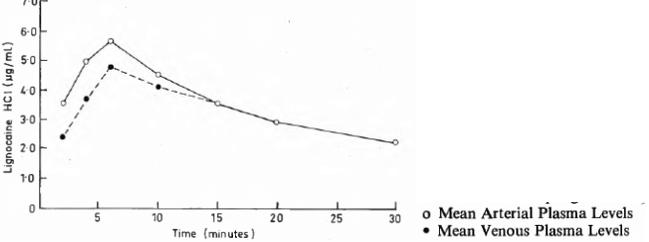
Dosing recommendation for children aged 4 years and above:

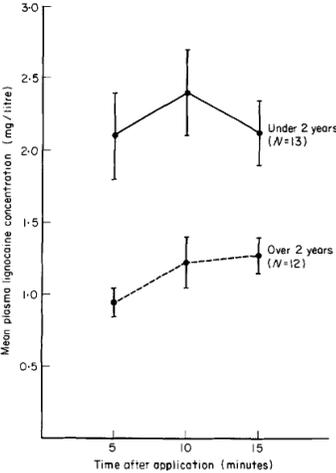
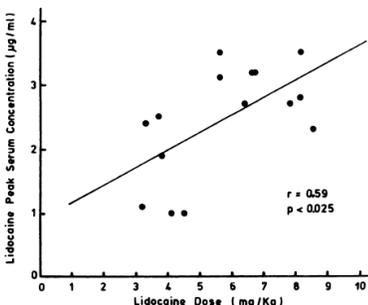
- Give maximum 6 gelsollets/lozenges per day
- Spray only 2 or 3 times at each application 3 to 6 times per day.
- Use only 5 ml of the solution to rinse the mouth after meals in the morning and in the evening.

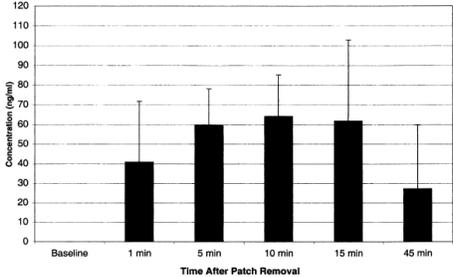
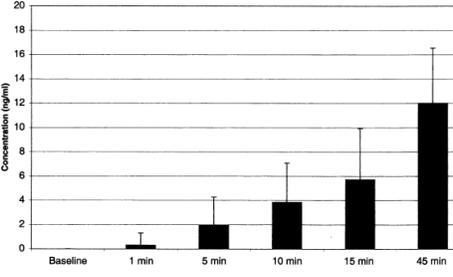
The MAH submitted 19 published studies, 9 internal reports (concerning benzoxonium only) and 3 PSURs (concerning the combination benzoxonium/lidocaine) together with an Overview. The studies considered relevant are described below. No paediatric pharmacokinetic, paediatric pharmacodynamic or paediatric clinical efficacy studies have been performed with the benzoxonium/lidocaine combination product for oral use by the MAH.

Pharmacokinetics of lidocaine in children

Study/ Objective/ Type of study	Treatments	Subjects No (M/F)/ Age (range)/ Weight (range)/ Type	Main outcome
<p>Finholt et al, 1986</p> <p>To determine lidocaine pharmacokinetics after intravenous administration in young children during general anaesthesia</p> <p>Single dose PK study</p>	<p>Lidocaine 1 mg/kg infused <u>intravenously</u> over 30 sec. Arterial blood sampling: 0.5, 1, 2, 4, 5, 19, 15, 30, 60, 90 and 120 min after lidocaine administration</p>	<p>10 children (0.5-3 years; 4.5-14 kg)</p> <p>8 adults (18-51 years; 48-82)</p> <p>General anaesthesia (halothane (1.5% inspired), nitrous oxide (70% inspired) and oxygen)</p>	<p>PK results: $t_{1/2 \alpha}$ (min): 3.2±1.4 (children); 3.6±1.2 (adult) $t_{1/2 \beta}$ (min): 58±19 (children); 43±16 (adult) V_1 (L/kg): 0.22±0.11 min (children); 0.16±0.09 min (adult) V_d area (L/kg): 1.11±0.34 min (children); 0.71±0.28 min (adult) Cl ($ml \cdot kg^{-1} \cdot min^{-1}$): 11.1±1.8 min (children) 9.8±1.4 min (adult)</p>  <p>Conclusion: Lidocaine distribution and elimination in young children proceeds in the same manner as adults. In 9 out of 10 children peak levels did not reach levels considered toxic in adults and there were no apparent toxic reactions in the study.</p>
<p>Eyres et al, 1978</p> <p>To determine whether commonly accepted dosages used in children produces blood levels within safe range</p> <p>Single dose study</p>	<p>Lidocaine HCl 1%, 4 mg/kg for <u>caudal and subcutaneous</u> administration.</p> <p>Lidocaine HCl 4%, 4 mg/kg for <u>topical administration</u></p> <p>Bupivacaine HCl 0.5%, 2 mg/kg for caudal and subcutaneous</p>	<p>73 children 5 days-15 years (M/F?) weight range?</p> <p>Children having routine elective procedures</p>	<p>Summary of mean plasma levels</p>

	<p>administration</p> <p>Blood sampling at baseline, at 5, 10, 15, 20, 30, 45, 60 and 90 min after administration.</p>		 <p>Conclusion: The authors conclude that the highest peak levels were in children under 3 years following tracheal spray but all blood levels were below accepted toxic adult levels for anaesthetised patients. No toxic manifestations were seen.</p>															
<p>Eyres et al, 1983</p> <p>To determine whether commonly accepted dosages used in children produces blood levels within safe range</p> <p>Single dose study</p>	<p>Lidocaine HCl 4, 4 mg/kg %, <u>topical laryngeal spray application</u> (larynx and immediate subglottic area)</p> <p>Blood sampling (venous) at baseline, at 2, 4, 6, 10, 15, 20 and 30 min after application. Parallel sampling using venous and arterial sampling in 12 patients.</p>	<p>96 children (M/F?) 2 weeks to 12 years, weight range?</p> <p>Children undergoing general surgery</p> <p>Anesthesia (tubocurarine, nitrous oxide/oxygen)</p>	<p>Peak plasma concentrations and time to peak concentration</p> <table border="1" data-bbox="776 745 1226 913"> <thead> <tr> <th>Age (years)</th> <th>Peak plasma concentration (µg/ml)</th> <th>Time to peak concentration (min.)</th> </tr> </thead> <tbody> <tr> <td><1</td> <td>4.3 (1.9)</td> <td>5.8 (2.5)</td> </tr> <tr> <td>1-3</td> <td>5.7 (2.0)</td> <td>6.5 (2.4)</td> </tr> <tr> <td>3-5</td> <td>5.3 (1.4)</td> <td>8.9 (3.7)</td> </tr> <tr> <td>> 5</td> <td>5.3 (2.0)</td> <td>11.7 (4.3)</td> </tr> </tbody> </table> <p>Mean plasma concentrations against time for 12 patients having simultaneously arterial and venous sampling</p>  <p>Conclusion: A more rapid uptake in younger children although peak plasma levels were similar. High blood levels (8 µg/ml) appeared randomly in all age groups, however, no evidence of systemic toxicity observed. A difference between arterial and venous plasma levels occurred during the first 10 minutes. The authors conclude that a dose of 4 mg/kg via tracheal spray is safe in anesthetised children.</p>	Age (years)	Peak plasma concentration (µg/ml)	Time to peak concentration (min.)	<1	4.3 (1.9)	5.8 (2.5)	1-3	5.7 (2.0)	6.5 (2.4)	3-5	5.3 (1.4)	8.9 (3.7)	> 5	5.3 (2.0)	11.7 (4.3)
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<p>Whittet et al, 1988</p> <p>To correlate the plasma levels of lidocaine, following local application to the upper airways, to the moistness of the mucosa</p> <p>Single dose study</p>	<p>Lidocaine (4 mg/kg) <u>was sprayed in the upper airways</u> (the dose was directed in equal portions to the supraglottic, glottis and subglottic regions).</p> <p>Blood sampling at 5, 10 and 15 min after spraying.</p>	<p>30 children (M/F?)</p> <p>8 months to 10 years 7-27 kg</p> <p>Children undergoing endoscopy under general anaesthesia (cyclopropane in oxygen or</p>	<p>Data from 25 children available.</p> <p>Mucosal moistness of the upper airway showed a statistically significantly, but inverse, correlation with the plasma levels of lidocaine.</p> <p>Children below 2 years of age were found to have statistically significantly ($p < 0.05$) higher plasma levels than older children. Plasma level of 5.6 µg/ml observed in one 6-month old child.</p> <p>Mean plasma lidocaine levels</p>															

		halothane in oxygen)	 <p>Mean plasma lignocaine concentration (mg/litre)</p> <p>Time after application (minutes)</p> <p>Under 2 years (N=13)</p> <p>Over 2 years (N=12)</p> <p>No signs of systemic toxicity were observed.</p> <p>Conclusion: According to the authors topical lidocaine as an adjunct to general anaesthesia for upper airway assessment seems to be safe. However, in children under 2 years of age a reduced dose of lidocaine should be considered since higher plasma levels are reached.</p>
<p>Amitai et al, 1990</p> <p>To evaluate the safety of topical lidocaine anaesthesia in children during bronchoscopy.</p> <p>Single dose study</p>	<p>Lidocaine 5.7 ± 0.5 mg/kg (range 3.2 to 8.5 mg/kg) administered to <u>nose, larynx and bronchial tree</u> over 9 to 45 (mean +/- SEM = 20 +/- 2.7) minutes.</p>	<p>15 children (M/F?)</p> <p>2.5 years (3 months-9.5 years, weight range?)</p> <p>Children undergoing flexible fiberoptic bronchoscopy</p>	<p>No complications occurred during the procedure. Peak serum lidocaine concentrations (SLC) were 1-3.5 (mean +/- SEM = 2.5 +/- 0.2) µg/ml. The Vd beta was 1.79 +/- 0.19 L/kg, the t1/2 beta was 109 +/- 12 minutes, and the total body clearance 12.2 +/- 1.1 ml/min/kg. Peak SLC correlated well with the dose expressed as mg/kg (r = 0.59, p less than 0.025), and even better when related to body surface area (r = 0.63, p less than 0.01).</p>  <p>Lidocaine Peak Serum Concentration (µg/ml)</p> <p>Lidocaine Dose (mg/Kg)</p> <p>r = 0.59 p < 0.025</p> <p>Conclusion: The authors conclude that lidocaine doses up to 8.5 mg/kg proved safe. Lidocaine dose up to 7 mg/kg appears to be safe provided that it does not exceed an upper limit of 175 mg/m2 and is gradually administered over a minimum of 15 minutes. Doses of 7-8.5 mg/kg appear to be safe when administered over longer periods.</p>
<p>Leopold et al, 2002</p> <p>To determine whether plasma lidocaine concentrations generated by a transmucosal patch, containing 46.1 mg of lidocaine,</p>	<p>Lidocaine (46.1 mg) <u>transmucosal patch</u> was placed on the mucosa overlying the maxillary incisors after nasotracheal intubation.</p>	<p>11 children (M/F?)</p> <p>2.7 years</p> <p>18.5 kg (12.6-26.3 kg)</p> <p>General anaesthesia for comprehensive dental</p>	<p>Mean peak plasma lidocaine concentration was 82±26 ng/mL, ranging from 41 to 128 ng/mL. The mean time at which peak plasma lidocaine concentration was attained was 9±1 minutes, ranging from 1 to 15 minutes.</p> <p>Mean plasma lidocaine concentrations</p>

<p>are within a safe range for children.</p> <p>Single dose PK study</p>	<p>Duration of patch 5 minutes.</p> <p>Blood sampling for lidocaine and Monoethylglycin exylide (MEGX) plasma levels at baseline and at 1, 5, 10, 15 and 45 minutes after patch application.</p>	<p>care</p>	 <p>The mean maximum plasma MEGX concentration was 11.98 ± 1.55 ng/mL, ranging from 5.4 to 18.98 ng/mL. All subjects demonstrated a maximum MEGX level at the latest time point, 45 minutes.</p> <p>Mean plasma MEGX concentrations</p>  <p><i>Safety and local tolerability</i></p> <p>No tissue discoloration, swelling or sloughing was note in association with patch application in any of the subjects. In addition, no drug-related adverse events were associated with patch application. None of the subjects experienced any complications during the general anaesthetic procedure or during the dental treatment.</p> <p><u>Conclusion:</u> The lidocaine and MEGX absorbed from an oral mucoadhesive patch, containing 46.1 mg lidocaine, achieved systemic levels which did not exhibit safety concerns in children 2-7 years undergoing comprehensive dental care under general anaesthesia. However, plasma concentrations were much higher (4-5 times higher) in children than in adults and were high enough to require inclusion in the calculation of total lidocaine administered to a pediatric patient. The local tolerability of the patch was good and no adverse events were reported.</p>
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Lignocaine=Lidocaine

The MAH submitted published paediatric data covering both active substances, however, for the benzoxonium/lidocaine combination there are no pharmacokinetic data available. Considering the present procedure this assessment has focused on the studies with lidocaine only.

In the submitted studies, lidocaine doses of 1 to 8 mg/kg was administered via intravenous, caudal, subcutaneous or topical application (nose, upper airways) to children undergoing different investigational/operational procedures. The average peak plasma values were within the range of 1-7 µg/mL (after a single dose of 1-8 mg/kg) for most of the studies. Although some of the children were exposed to toxic levels of lidocaine no toxic effects were observed in the children. Initial symptoms of CNS toxicity are considered to begin at 5 µg/mL.

The results from the studies indicate that higher peak plasma levels are reached when lidocaine is applied topically on mucous membranes (nose, upper airways) to younger children (less than 3 years) when compared to older children and adults.

PK data from a transoral delivery patch (46.1 mg) is also available from children aged 2-7 years undergoing dental care. The transoral delivery patch resulted in plasma levels of 82 ng/mL which is far from the plasma levels that induce toxicity.

No pharmacokinetic data is available for Orofar (benzoxonium/lidocaine combination). The maximum recommended lidocaine doses for Orofar are 6 mg/day (lozenges, gelsollets), 3.8 mg/day (oromucosal spray, assuming 0.140 µl/spray) and 5 mg/day oromucosal solution. Considering that the average weight of a 4 year old child is around 16 kg, the administration of doses of 6 mg will correspond to 0.38 mg/kg for the total daily dose. Although no pharmacokinetic data is available for Orofar the anticipated plasma levels would clearly be below the plasma levels inducing toxic effects in a child. Thus, no safety concerns would be expected.

Clinical efficacy and safety

Intraoperative local anaesthesia for paediatric oral surgery pain – a randomized controlled trial. Coulthard P, Rolfe S, Mackie C, Gazal G, Morton M, Jackson-Leech D (2006) , Int. J. Oral Maxillofac. Surg. 2006; 35: 1114- 1119.

Trial objectives: Improve pain relief in children, following oral surgery under general anaesthesia

Trial design: This was a randomized, controlled single-center study in 142 children, aged 4-12 years, who were scheduled for dental extractions under general anaesthesia.

Population: Male and female children, aged 4-12 years, scheduled for extraction of 1-10 teeth. Subjects were excluded if they had a known hypersensitivity or allergy to lidocaine or acetaminophen.

Study drug: Randomized assignment to one of two treatments:

- 2 ml of 2% lidocaine with 1:200 000 epinephrine (adrenalin) administered by buccal infiltration adjacent to the teeth to be removed.
- 2 ml of placebo (0.9% Sodium Chloride) administered by buccal infiltration adjacent to the teeth to be removed.

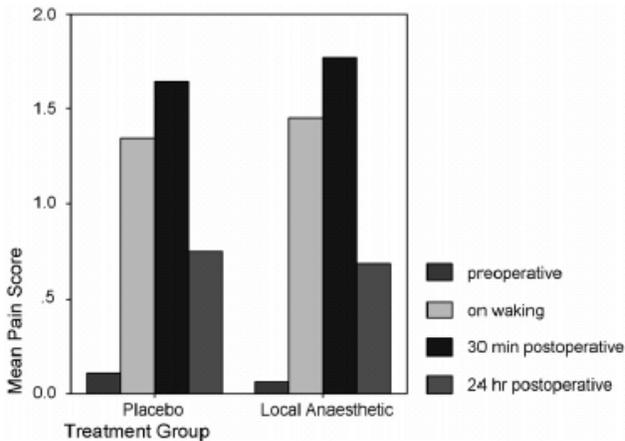
Results:

142 children were recruited. Data was incomplete in 3 children, providing evaluable data for 70 children in the active group and 69 in the placebo group.

Efficacy

Pre- and postoperative pain and distress were measured on a 0-4 point picture scale (no, mild, moderate, severe and very severe pain) before surgery and upon awakening from anaesthesia, after 30 minutes and after 24 hours.

Fig. Bar graph showing mean pain score for local anaesthetic and placebo groups.



There was statistically no significant difference between the groups for pain scores recorded preoperatively, on waking and at 30 minutes. Severe pain scores were recorded for 14% of treatment and 12% of control patients and very severe scores for 13% of treatment and 10% of control patients upon awakening. These rates were similar after 30 minutes but improved after 24 hours.

Safety

Except for lip/cheek biting injuries in 4 subjects reported 24 hours after surgery (3 in the active group and 1 in the placebo group), no adverse events were reported.

To conclude, in this placebo controlled study with 142 children there were no statistically significant difference between the placebo and the lidocaine/ epinephrine (adrenalin) treated groups. Thus, the lidocaine/ epinephrine (adrenalin) was not effective in reducing the postoperative pain or distress in children following oral surgery. In conclusion, there is no new information from this study leading to modifications of SmPC.

Does topical lidocaine with adrenaline have an effect on morbidity in paediatric tonsillectomy? Egeli E, Harputluoglu U, Oghan F, Demiraran Y, Guclu E, Ozturk O (2005), International Journal of Pediatric Otorhinolaryngology 69, 811-815

Trial objectives: Evaluate the efficacy of lidocaine with adrenaline on post-operative morbidity in paediatric patients after tonsillectomy.

Trial design: This was a double-blind randomized controlled single centre study in 40 children scheduled for tonsillectomy.

Population: Forty male and female children, aged 4-16 years, admitted for tonsillectomy.

Study drug: Randomized assignment to one of two treatments:

- 2 swabs soaked each with 2 ml lidocaine 20 mg/ml + Adrenaline 0.0125 mg/ml tightly packed into the tonsillar fossae
- 2 swabs soaked each with 2 ml saline solution tightly packed into the tonsillar fossae

All subjects received postoperatively acetaminophen 10-20 ml and Amoxicillin suspension 5- 10 mg four times daily.

Results:

Forty patients (13 females and 27 males), in the age range 4-16 years were evaluable for efficacy.

Efficacy

Pain scores were recorded at 1, 5, 17, 17 and 21 hours on 1st, 2nd, 3rd, 4th, 5th and 6th day postoperatively, using Mc Grath's face scale. There was no statistically significant difference between the active and the placebo group on post-operative pain relief or the other postoperative parameters, such as nausea, fever, vomiting, halitosis, bleeding, otalgia or trismus.

Safety

There were no complications or other adverse events reported for the lidocaine/adrenaline group.

To conclude, in this small double blind placebo controlled clinical study with 40 children there were no statistically significant difference with regard to reducing morbidity in pediatric tonsil surgery between the placebo and the lidocaine/adrenaline treatment. In conclusion, no SmPC modifications are suggested based on the data from this study.

A comparison between Articaine HCl and Lidocaine HCl in pediatric dental patients. Malamed SF, Gagnon S, Leblanc D (2000) Pediatric Dentistry 22; 4: 307-311.

Trial objectives: Compare the safety and efficacy of Articaine HCl (4% with epinephrine 1: 100000) with lidocaine HCl (2% with epinephrine 1: 100000) as a local anaesthetic for children undergoing general dental procedures.

Trial design: 3 identical single-dose, randomized, double-blind, active controlled multi-center studies were performed involving multiple sites, including subjects 4-79 years of age. A subgroup of 50 subjects 4 to <13 years of age were treated at a total of 7 sites in the United Kingdom and USA.

Only data from children is described below.

Population: Children of both sexes, aged 4 to <13 years scheduled to undergo general dental procedures.

Study drug: Randomized assignment in a 2.5:1 ratio of:

- Articaine HCl (4% with epinephrine 1: 100 000), lowest effective dose not to exceed 7.0 mg/kg body weight (50 subjects).
- Lidocaine HCl (2% with epinephrine 1: 100 000), lowest effective dose not to exceed 7.0 mg/kg body weight (20 subjects).

Results:

Paediatric patients received equal volumes, but higher mg/kg doses, of Articaine than lidocaine during both simple and complex dental procedures.

Efficacy

Average VAS (Visual Analogue Scale) scores (from 0-10 cm) for pain during procedure for Articaine and lidocaine are presented in Table below.

Table 3. Summary of VAS Pain Scores (0–10 cm) Stratified by Complexity of Procedure

Procedure	4% articaine + epinephrine 1:100,000		2% lidocaine + epinephrine 1:100,000		p-value*
	Simple	Complex	Simple	Complex	
Number of subjects	43	7	18	2	
Investigator score (cm)					0.569
Mean	0.4	0.6	0.3	2.8	
Range	0–4.1	0–2.1	0–1.2	2.2–3.4	
Patient score (cm)					0.416
Mean	0.5	1.1	0.7	2.3	
Range	0–5.5	0–2.5	0–3.0	0–4.5	

* Two-sided p-value from a Kruskal-Wallis test comparing treatment groups

Both compounds were effective in suppressing pain due to both simple and complex dental procedures.

Safety

Safety was evaluated by measuring vital signs before and after administration of the local anaesthetic (1 and 5 minutes post-medication and at the end of the procedure) and by assessing adverse events throughout the study (telephone follow-up at 24 hours and 7 days after the procedure).

No serious adverse events related to the study medication occurred. At least one minor and non-serious adverse event was reported by 8% (4/50) of Articaine subjects and 10% (2/20) of lidocaine subjects. In the lidocaine group, the only minor adverse event reported was postprocedural pain. See Table below.

Table 4. Adverse Events Reported by Patients 4 to <13 Years Old

Body system/Adverse event	Articaine 4% with epinephrine 1:100,000 (N = 50)	Lidocaine 2% with epinephrine 1:100,000 (N = 20)
Patients with at least one event	4 (8%)	2 (10%)
Body as a whole		
Accidental injury	1 (2%)	0
Headache	1 (2%)	0
Injection site pain	1 (2%)	0
Pain	1 (2%)	2 (10%)

Significant changes in vital signs did not occur in any treatment group.

To conclude, lidocaine/adrenaline treatment was compared to articaine/adrenaline treatment in this double blind controlled trial where 70 children, 4-13 years, were undergoing dental procedures. Both treatments provided total pain relief during most dental procedures. There was no statistically significant difference between the effects of the two treatments. The only minor and non-serious adverse event noted in the lidocaine group was post-procedural pain. Lidocaine/adrenaline products are already approved in most countries as a local anaesthetic for general dental procedures.

Topical analgesia for acute otitis media (Review) Foxlee R, Johansson AC, Wejfalk J, Dawkins J, Dooley L, DeMar C, Cochrane Database of Systematic Reviews. 2, 2009

Background: Acute otitis media (AOM) is a spontaneously remitting disease for which pain is the most distressing symptom. Antibiotics are now known to have less benefit than previously assumed.

Objectives: To assess the effectiveness of topical analgesia for AOM.

Search strategy: Authors searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2009, issue 1) which contains the Acute Respiratory Infection (ARI) Group's Specialised Register, MEDLINE (2006 to January Week 2 2009), EMBASE (2006 to 2009 Week 03), CINAHL (2006 to January Week 2 2009) and AMED (1985 to January 2009).

Selection criteria: Double-blind randomised controlled trial (RCTs) or quasi-RCTs comparing an otic preparation with an analgesic effect (excluding antibiotics) versus placebo or an otic preparation with an analgesic effect (excluding antibiotics) versus any other otic preparation with an analgesic effect, in adults or children presenting at primary care settings with AOM without perforation.

Data collection and analysis: Three review authors independently screened studies and assesses trial quality. Data were independently extracted from selected trials. Attempts to obtain additional information from authors of three trials were unsuccessful.

Main results:

Five trials of children aged three to 18 years met our criteria. Two studies (117 patients) compared anaesthetic ear drops versus placebo immediately at diagnosis. All children received some form of oral pain relief. There was a statistically significant difference in the proportion of children achieving a 50% reduction in pain in favour of anaesthetic drops 10 minutes after instillation (relative risk (RR) 2.13, 95% CI 1.19 to 3.80) and 30 minutes after instillation (RR 1.43, 95% CI 1.12 to 1.81) on the day AOM was diagnosed but not at 20 minutes (RR 1.24, 95% CI 0.88 to 1.74). All patients received some form of oral pain relief. Three trials (274 patients) compared anaesthetic ear drops with naturopathic herbal ear drops. Naturopathic drops were favoured 15 and 30 minutes after instillation, one to three days after diagnosis, but the differences were not statistically significant. Only two of which addressed the most relevant question of primary effectiveness, which provided limited evidence that ear drops are effective 30 minutes after administration in older children with AOM. Uncertainty exists as to the magnitude of this effect and more high quality studies are needed.

To conclude, more studies are needed to convincingly show a pain relief effect in the treatment of acute otitis media in children between 3-18 years. Thus, there is no new significant information leading to proposed modifications of the SmPC from this review of data.

Pain relief for neonatal circumcision (Review). Brady-Fryer B, Wiebe N, Lander JA, Cochrane Database of Systematic Reviews. 2, 2009

Background: Circumcision is a painful procedure that many newborn males undergo in the first few days after birth. Interventions are available to reduce pain at circumcision; however, many newborns are circumcised without pain management.

Objectives: The objective of this review was to assess the effectiveness and safety of interventions for reducing pain at neonatal circumcision.

Search strategy: Authors searched Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, Issue 2, 2004), MEDLINE (1966 - April 2004), EMBASE (1988 - 2004 week 19), CINAHL (1982 - May week 1 2004), Dissertation Abstracts (1986 - May 2004), Proceedings of the World Congress on Pain (1993 - 1999), and reference lists of articles. Language restrictions were not imposed.

Selection criteria: Randomised controlled trials comparing pain interventions with placebo or no treatment or comparing two active pain interventions in male term or preterm infants undergoing circumcision.

Data collection and analysis: Two independent reviewers assessed trial quality and extracted data. Ten authors were contacted for additional information. Adverse effects information was obtained from the trial reports. For meta-analysis, data on a continuous scale were reported as weighted mean difference (WMD) or, when the units were not compatible, as standardized mean difference.

Main results

Thirty-five trials involving 1,997 newborns were included. Thirty-three trials enrolled healthy, full term neonates, and two enrolled infants born preterm. Fourteen trials involving 592 newborns compared dorsal penile nerve block (DPNB) with placebo or no treatment. Compared to placebo/no treatment, DPNB demonstrated significantly lower heart rate [WMD -35 bpm, 95% CI -41 to -30], decreased time crying [WMD -54 %, 95% CI -64 to -44], and increased oxygen saturation [WMD 3.7 %, 95% CI 2.7 to 3.7]. Six trials involving 200 newborns compared eutectic mixture of analgesics (EMLA) with placebo. EMLA demonstrated significantly lower facial action scores [WMD -46.5, 95% CI -80.4 to -12.6], decreased time crying [WMD - 15.2 %, 95% CI -21 to -9.3] and lower heart rate [WMD - 15 bpm, 95% CI -19 to -10]. DPNB, compared with EMLA in three trials involving 139 newborns (133 of whom were included in the analysis), demonstrated significantly lower heart rate [WMD -17 bpm, 95% CI -23 to -11] and pain scores. When compared with sucrose in two trials involving 127 newborns, DPNB demonstrated less time crying [MD -166 s, 95% CI -211 to -121], and lower heart rate [WMD -27 bpm, 95% CI -33 to -20]. Results obtained for trials comparing oral sucrose and oral analgesics to placebo, and trials of environmental modification were either inconsistent or were not significantly different.

Adverse effects included gagging, choking, and emesis in placebo/untreated groups. Minor bleeding, swelling and hematoma were reported with DPNB. Erythema and mild skin pallor were observed with the use of EMLA. Methaemoglobin levels were evaluated in two trials of EMLA, and results were within normal limits.

To conclude, EMLA was less effective for reducing pain at neonatal circumcision than dorsal penile nerve block (DPNP) but the pain was not completely eliminated by either treatment. There might also be some difficulties with the application and the time required for maximum anaesthetic effect when using EMLA/lidocaine products, thus, further data is needed. Adverse events with EMLA use was transient skin reaction such as erythema and mild skin pallor. Overall, it can be considered that no convincing new data emerged that would lead to any SmPC change.

A Systematic Review of Lidocaine-Prilocaine Cream (EMLA) in the Treatment of Acute Pain in Neonates

Taddio A, Ohlsson A, Einarson TR, Stevens B, Koren G (1998) , Pediatrics;101:e1

Objective: Neonates routinely undergo painful cutaneous procedures as part of their medical treatment. Lidocaine-prilocaine 5% cream (EMLA) is a topical anesthetic that may be useful for diminishing the pain from these procedures. EMLA is routinely used in children and adults. There is substantial apprehension about its use in neonates because of concerns that it may cause methemoglobinemia. The objective of this review was to determine the efficacy and safety of EMLA as an analgesic for procedural pain treatment in neonates and provide evidence-based recommendations for clinical practice.

Methods: Systematic review techniques were used. Studies were identified using manual and computeraided searches (Medline, EMBASE, Reference Update, personal files, scientific meeting proceedings). Behavioral (eg, facial action, crying) and physiologic (eg, heart rate, oxygen saturation, blood pressure, respiratory rate) outcome data from prospective nonrandomized controlled studies and randomized controlled trials in fullterm and preterm neonates were accepted for inclusion to establish efficacy of EMLA. The risk of methemoglobinemia (defined as methemoglobin concentration >5% and requiring medical intervention) was estimated from all prospective studies.

Results:

Eleven studies of the efficacy of EMLA were included in the analysis. Infant gestational age at the time of delivery ranged from 26 weeks to full-term. Two studies included data from both neonates and older infants. The following procedures were studied: circumcision (n=3), heel lancing (n=4), venipuncture (n=1), venipuncture and arterial puncture (n =1), lumbar puncture (n =1), and percutaneous venous catheter placement (n =1). Nine studies were randomized controlled trials. The total sample size for each study ranged from 13 to 110 neonates. The dose of EMLA used was 0.5 g to 2 g in 9 studies, and was not specified in the others. The duration of application ranged from 10 minutes to 3 hours. The three studies that investigated the efficacy of EMLA for decreasing the pain of circumcision used a randomized controlled trial design. All of them demonstrated significantly reduced crying time during the procedure in the infants in the EMLA group compared with the infants in the control group. Facial grimacing, assessed in two of the studies, was also significantly lower in the EMLA group. Using meta-analytic techniques, the heart rate outcome data for two studies was summarized. Increases in heart rate compared with baseline values were 12 to 27 beats per minute less for the EMLA group than in the placebo group during various stages of the surgical procedure.

Three studies that investigated the pain from heel lancing were randomized controlled trials; the other was a nonrandomized controlled study. None demonstrated a significant benefit of EMLA for any of the outcome measures used to assess pain (ie, behavioural pain scores, infant crying, heart rate, blood pressure, respiratory rate, oxygenation parameters). One randomized controlled study of the pain from venipuncture showed that infants treated with EMLA had significantly lower heart rates and cry duration compared with infants treated with a placebo. In one nonrandomized study, a significantly lower behavioral pain score was observed for infants treated with EMLA compared with the control group. Infant heart rate, however, did not differ between the groups. In one randomized controlled study of pain from percutaneous venous catheter placement, EMLA resulted in a significantly lower increase in heart rate and respiratory rate. Behavioral pain scores were significantly lower during arterial puncture in one nonrandomized controlled study. EMLA did not reduce physiologic changes or behavioral pain scores in one randomized controlled trial in infants undergoing lumbar puncture. Meta-analytic techniques revealed that methemoglobin concentrations did not differ between EMLA-treated and placebo-treated infants (weighted mean difference, 20.11%; 95% confidence interval, 20.31% to 0.10%). The incidence of clinically important methemoglobinemia from all prospective studies was 0% (95% confidence interval, 0.0% to 0.2%). There was insufficient data to assess the risk with multiple doses of EMLA. Four studies measured concentrations of lidocaine in the

plasma of neonates who had been treated with EMLA. In all cases, concentrations were <0.3 mg/mL. Three studies that measured prilocaine detected <0.1 mg/mL.

In conclusion, EMLA diminishes pain during circumcision. It may also diminish the pain from venipuncture, arterial puncture, and percutaneous venous catheter placement; however, efficacy data for these procedures are limited. EMLA does not diminish the pain from heel lancing. Based on available data, EMLA is recommended for the treatment of pain from circumcision but not heel lance. There is insufficient data to recommend its use for other procedures. Single doses do not cause methemoglobinemia. Additional research is recommended in neonates before EMLA is used routinely for procedures other than circumcision and to determine the safety of repeated administration.

To conclude, with regard to the circumcision procedure, the data showed that infants treated with EMLA had a reduced crying time during the procedure when compared with the infants in the control group. However, there might be some difficulties with the application and the time required for maximum anaesthetic effect when using EMLA. EMLA is not specifically indicated for use in circumcision procedures, although the indication might be considered to cover also this use. No modification of the indication is warranted on the basis of these data.

The efficacy of EMLA was insufficiently demonstrated in this review (dated 1998) to be used in other procedures, i.e. venipuncture, arterial puncture, percutaneous venous catheter placement, and heel lance.

The safety profile was similar between the EMLA and the control groups. Single doses do not cause methemoglobinemia but no data is available after repeated administration and this is considered to be a deficiency.

Thus, no new indications are suggested based on these data.

Post-marketing experience with benzoxonium/lidocaine (Orofar) in Children.

PSUR 1 [Bovey A. 2001] (13 June 1996 to 12 June 2001), PSUR 2 [Bovey A. 2006] (13 June 2001 to 12 June 2006), PSUR Addendum Report [Casado JM. 2007] (13 June 2006 to 30 April 2007), Line listings in preparation of PSUR 3 (13 June 2006 to 12 June 2009).

Safety Assessment in children (<18 years of age)

Of all 29 cases received between 1 January 1996 and 12 June 2009, two non-serious and one serious case were reported in patients under 18 years. The adverse events were “stomatitis” (non serious non serious in two cases and “tongue oedema” (serious) reported in this age group (14 and 17 years) and may be an expression of a local irritation and oedema of the throat, respectively as described in section 4.8 of the current Core Summary of Product Characteristics (05 June 2009). Further, the safety information received during the review period for patients under 18 years is consistent with the established safety profile of Orofar.

To conclude, the safety information received during the review period for patients under 18 years is consistent with the established safety profile of Orofar as reflected in the current reference safety information and overall safety assessment. From the first approval, twenty-nine case reports of the various Orofar presentations were received worldwide with a patient exposure of more than 46 million patients. The safety profile is considered well established and no new safety signals have been detected in all patient populations, including the pediatric population.

Overall conclusion

Based on review of available documentation on efficacy and safety, data remain in line with the current Core SmPC. The safety profile is considered well established and no new safety signals have been detected in all patient populations, including the pediatric population. The MAH proposed some slight SmPC modifications during the procedure. In line with the SmPC guideline: the following SPC modifications are proposed:

Section 4.1

The following should be included:

“Orofar is indicated in children and adolescents aged 4 to 18 years of age” alternatively **“Orofar is indicated in children and adolescents aged 6 to 18 years of age”** depending on the already approved age range in children in the concerned member state.

Section 4.4

The following should be included:

“Pediatric population:”

“Orofar should not be used in children aged less than 4 years.” alternatively **“Orofar should not be used in children aged less than 6 years.”** depending on the already approved age range in children in the concerned member state.

Section 4.8

The following should be included:

“Pediatric population:”

“Frequency type and severity of adverse reactions in children are expected to be same as in adults.”

Strepsils +Plus (Reckitt Benckiser)

The product is a combination of 0.6 mg amylmetacresol, 1.2 mg 2, 4-dichlorobenzyl alcohol, and 10mg lidocaine hydrochloride (2 mg in France) and available as lozenges.

The combination product is indicated for the symptomatic relief of mouth and throat infections including severe sore throat. Strepsils +Plus lozenges are indicated for adults and children over the age of 12 years old.

The dosing recommendation for children over 12 years are;

One lozenge to be dissolved slowly in the mouth every 2 hours as required. For oral administration. Children under 12 years: not recommended for children under 12 years.

The MAH has submitted a critical Overview and referred to a number of studies in the Overview.

The MAH has provided paediatric data for the Strepsils Plus product, which contains lidocaine, to the Spanish health authority and to EMA in January 2008 based on the requirement to provide supporting clinical documentation for the paediatric patient population.

A detailed literature search of published data on the administration of lidocaine products in children of varying ages, ranging from a newborn baby to children 18 years of age, has shown that based on the available pharmacokinetic, pharmacological, efficacy and safety information (as described in the Expert Report), the indications, contraindications and warnings included in the current SmPC for Strepsils Plus and the product labelling are valid and appropriate for paediatric use (children over 12 years).

The MAH has also submitted Study BH5002 (1996). The study is a single dose, parallel group, placebo controlled comparative study investigating the efficacy and safety of Strepsils Dual Action Anaesthetic Lozenge (DCBA, AMC and lidocaine), and Dimam Anti-Inflammatory Lozenge (benzydamine and cerylpyridinium chloride) in 208 evaluable patients 17 years or more with sore throats. The primary efficacy analysis indicated that there were no statistically significant differences ($p=0.1282$) between Strepsils Plus, Diffiam and placebo at the 15 minute post-dose assessment for sore throat pain intensity. However, in a secondary efficacy analysis of data at 30, 45 and 60 minutes, subjects receiving Strepsils Plus recorded significantly lower pain scores than those receiving placebo ($p=0.0223$, $p=0.0094$, $p=0.0162$ respectively).

Efficacy studies have not been conducted in paediatric populations for the treatment of sore mouth other than some trials that included children aged 16 years submitted within the registration application.

From July 1994 to 31 July 2007, a cumulative total of 19 serious and 56 non-serious adverse events were reported as either spontaneous medically confirmed reports or regulatory reports or from clinical studies (Ref: PSUR Strepsils Core, Aug 06 – July 07, AMC & DCBA, not submitted).

The MAH has submitted the PSUR covering 01st September 2009 to 31st August 2010 (Data Lock Point, DLP). Since launch till DLP, 24 serious unlisted ADRs were received for Strepsils Pain Relief Plus Lozenges. No safety concerns were identified.

Adverse events reported in children and adolescence is presented below in the Table.

AE System Organ Class	AE Preferred Term	Possible	Unlikely	Not assessed	Grand Total
Gastrointestinal disorders	Vomiting			1	1
<i>Gastrointestinal disorders Total</i>				<i>1</i>	<i>1</i>
General disorders and administration site conditions	Drug ineffective	1			1
<i>General disorders and administration site conditions Total</i>		<i>1</i>			<i>1</i>
Immune system disorders	Anaphylactic reaction			1	1
<i>Immune system disorders Total</i>				<i>1</i>	<i>1</i>
Psychiatric disorders	Hallucination		1		1
	Nightmare		1		1
<i>Psychiatric disorders Total</i>			<i>2</i>		<i>2</i>
Respiratory, thoracic and mediastinal disorders	Acute respiratory distress syndrome	1			1
	Laryngeal oedema	1			1
<i>Respiratory, thoracic and mediastinal disorders Total</i>		<i>2</i>			<i>2</i>
Grand Total		3	2	2	7

There have only been 7 events reported in 12-18 year olds in the period from launch to 31st January 2011 for the Strepsils Plus products. Sales are available from the previous PSURs with a period of 15th August 1995 (first worldwide launch date) to 31st August 2010, with total global sales of over 53.5 million packs.

No untoward effects on vital signs or following physical examination by investigating physicians have been reported after administration of Strepsils lozenges in clinical studies. The most commonly reported adverse events in clinical studies have been gastrointestinal disorders. The possibility of occasional hypersensitivity reactions and gastrointestinal discomfort associated with Strepsils lozenge over dosage is therefore acknowledged in the SmPC.

To conclude, the safety profile of Strepsils Plus is well established. No new safety concerns are identified in the adults, adolescents or children (from 12 years and older) in the most recent PSUR.

Overall conclusion

No specific efficacy studies have not been conducted for the product in paediatric populations for the treatment of sore mouth other than some trials that included children aged 16 years submitted within the registration application. The safety profile of Strepsils Plus is well established. In line with SmPC guideline the following SPC modifications are proposed:

Section 4.1

The following should be included:

“Strepsils Plus is indicated in children and adolescence aged 12 to 18 years of age”.

Xylonor (Septodont)

The following combination products are available:

Septodont is the manufacturer and the Marketing authorisation holder of several Lidocaine based products with an indication in anesthesia. There are two ranges: anaesthetic solutions for injection and topical anaesthesia.

The concerned products are listed in the table below:

Anaesthetic solution for injection		
Xylonor 3% Noradrenaline	Lidocaine 30 mg/ml Noradrenaline 0,004 mg/ml	Solution for injection
Xylonor 2% Noradrenaline	Lidocaine 20 mg/ml Noradrenaline 0,004 mg/ml	Solution for injection
Xylonor 2% Special	Lidocaine 20 mg/ml Adrenaline 0,02 mg/ml	Solution for injection
Lignospan Special	Lidocaine 20 mg/ml Adrenaline 0,0125 mg/ml	Solution for injection
Topical anaesthetic		
XOgel Child	Lidocaine 50 mg/g Cetrimide 1.5 mg/g	Gingival gel
XOgel Adult	Lidocaine 50 mg/g Cetrimide 1.5 mg/g	Gingival gel
Xylonor gel	Lidocaine 50 mg/g Cetrimide 1.5 mg/g	Gingival gel
Xylonor solution	Lidocaine 50 mg/ml Cetrimide 1.5 mg/ml	Solution for dental use
Xylonor pellets	Lidocaine 50 mg/ml Cetrimide 1.5 mg/ml	Impregnated cotton pellets for dental use
Xylonor Spray	Lidocaine 150 mg/g Cetrimide 1.5 mg/g	Solution
Xylonor Spray N	Lidocaine 150 mg/g	Solution

The products “lidocaine/(nor)adrenaline” are available as solutions for injection whereas the “lidocaine/cetrimide” products are available as gel, solution, impregnated pellets with a solution and solution in atomizer.

The MAH has proposed to amend SmPC section 4.2 for the XYLONOR SPECIAL and XYLONOR NORADRENALINE.

The MAH has submitted an Overview. The studies which have not been described elsewhere related to the use of lidocaine as a local anaesthetic with a sufficient level of information is briefly described below.

A clinical study in children aged 8 to 15 years injected with buffered lidocaine presented a reduction in pain for intravenous placement (*Kennedy & Luhmann 2001*). Lidocaine in local anaesthesia is commonly used in children as topical (cream or patch) and local infiltration (*Maurice et al. 2002*). Various dosages are available from 1% and 2% with EMLA, 4% for ELA-Max cream to 10% for iontophoresis patch (*Goldman 2004; Pasero 2006; Stewart et al. 1998; Wong 2003*). The most serious complication with the use of EMLA which is an eutectic mixture of local anaesthetics (2.5% lidocaine and 2.5% prilocaine) is methemoglobinemia.

The pharmacokinetics of lidocaine in infants and children (between 3 months and 11 years old) was reported without adverse effects by *Gunter (2002)*. The peak concentration (C_{max}) for lidocaine after typical clinical doses is below the accepted toxic threshold of 5 to 6 µg/ml. In general, C_{max}, time to C_{max} (t_{max}), volume of distribution at steady state (V_{dss}), clearance and half-life (t_{1/2}) values in children are comparable to the values seen in adults.

Table - Pharmacokinetics of lidocaine in infants and children (Gunter 2002)

Route	No. of patients	Age	Dose (mg/kg)	C _{max} (mg/L)	t _{max} (min)	V _{dss} (L/kg)	Clearance (ml/min/kg)	t _{1/2} (min)	Reference
Epidural	10	3mo-4y	5	2.50					92
Caudal	10	7mo-7y	11	2.20 ± 0.26	45				93
Caudal	10	7mo-7y	5.5	0.80 ± 0.07	45				93
Caudal	11	3.0-9.5y	5	2.05 ± 0.08	28 ± 3	3.05 ± 0.40	15.4 ± 1.2	155 ± 32	94
Intravenous	10	6mo-3y	1	3.67		1.11 ± 0.34	11.1 ± 1.8	58 ± 19	95
Caudal ^a	10	2-7y	5	1.30 ± 0.08	30				96
Caudal ^b	10	2-7y	5	1.58 ± 0.11	30				96
Penile	12	3-11y	1	0.36 ± 0.08	27 ± 18				97
Tracheal	21	3mo-2y	0.9-2.6	1.05 ± 0.55					98

a Premedicated with midazolam.

b No premedication.

C_{max} = peak plasma concentration; mo = months; t_{max} = time to C_{max}; t_{1/2} = half-life; V_{dss} = volume of distribution at steady state; y = years.

Ref. 92. Miyabe M, Kakiuchi Y, Kihara S, et al. The plasma concentration of lidocaine's principal metabolite increases during continuous epidural anesthesia in infants and children. *Anesth Analg* 1998; 87: 1056-7; **Ref 93.** Takasaki M. Blood concentrations of lidocaine, mepivacaine and bupivacaine during caudal analgesia in children. *Acta Anaesthesiol Scand* 1984; 28: 211-4; **Ref 94.** Ecoffey C, Desparmet J, Maury M, et al. Pharmacokinetics of lignocaine in children following caudal anesthesia. *Br J Anaesth* 1984; 56: 1399-402; **Ref 95.** Finholt DA, Stürt JA, DiFazio CA, et al. Lidocaine pharmacokinetics in children during general anesthesia. *Anesth Analg* 1986; 65: 279-82; **Ref 96.** Giaufré E, Bruguerolle B, Morrison-Lacombe G, et al. The influence of midazolam on the plasma concentrations of bupivacaine and lidocaine after caudal injection of a mixture of the local anesthetics in children. *Acta Anaesthesiol Scand* 1990; 34: 44-6; **Ref 97.** Sfez M, Mapihan YL, Mazoit X, et al. Local anesthetic serum concentrations after penile nerve block in children. *Anesth Analg* 1990; 70: 423-6; **Ref 98.** Sitbon P, Laffon M, Lesage V, et al. Lidocaine plasma concentrations in pediatric patients after providing airway topical anesthesia from a calibrated device. *Anesth Analg* 1996; 82: 1003-6

Gunter (2002) further stated that lidocaine has a favourable toxicity profile and its uptake is decreased and duration of action increased with the addition of epinephrine. The maximum recommended single dose is 5 to 7 mg/kg (perhaps 8 to 10 mg/kg with epinephrine).

Three PSURs were submitted. Septodont has had marketed products containing lidocaine with or without vasoconstrictors for decades. For Lidocaine, from 2002- 2009, three cases were reported for children whereas more than 3 million of units were sold. No new specific areas of pharmacovigilance interest were identified which needed to be included in the SmPC. The MAH also concluded that the occurrence of gingival ulceration, blister and sloughing will be continued to be closely monitored for the lidocaine/cetrimide products.

Overall conclusion

The MAH has proposed to amend SmPC section 4.2 for the XYLONOR SPECIAL and XYLONOR NORADRENALINE with the inclusion of a new table. The maximum dose in dental

use was evaluated also for Xylestesin-A and it was noted that there was a difference in the maximum dose proposed; i.e., maximum dose in 5 mg/kg for Xylestesin-A and 2.2 mg/kg for Septodont/Xylonor.

Based on the information submitted by the different MAHs and the literature research by the Rapporteur it can be concluded that the scientific basis for paediatric posology regarding dental injection lidocaine analgesia is not firm. The MAH Septodont has suggested 2.0 mg/kg BW of lidocaine as a conservative dose. The Rapporteur is of the opinion (after studying available, admittedly limited, data) that a more appropriate conservative dose is in the vicinity of 1.33 mg/kg BW as earlier suggested by the MAH. However, the maximum recommended dose of 2.2 mg/kg BW is probably a calculation mistake, maybe due to a mix-up between kg and lb in the initial marketing approval procedure. The generally accepted recommended maximum dose for paediatric dental use reported in the literature is in the range of 4-5 mg/kg BW.

Thus, the following posology for paediatric injectable analgesia is suggested:

“The average dose to be used is in the range of 20 mg to 30 mg lidocaine hydrochloride per session. The dose in mg of lidocaine hydrochloride which can be administered in children may alternatively be calculated from the expression: child’s weight (in kilograms) x 1.33. Do not exceed the equivalent of 5 mg of lidocaine hydrochloride per kilogram of body weight.”

There is no absolute contraindication for injectable analgesia in children below 4 years of age, even if it is mostly found not optimal. The Rapporteur is of the opinion that the inclusion of the following information in Section 4.2 highly appropriate:

<Product> is indicated in adults and children. Special care has to be exercised when treating children below 4 years. The quantity to be injected should be determined by the age and weight of the child and the magnitude of the operation. The anaesthesia technique should be selected carefully. Painful anaesthesia techniques should be avoided. The behaviour of the child during treatment has to be monitored carefully.

With this information there will be a harmonization (at least partly) within the EU of the posology information of different dental lidocaine products.

In conclusion, the new table proposed by the MAH is not accepted. However, the following amendments of the already approved text are proposed for LIGNOSPAN 2% SPECIAL, XYLONOR 2% NORADRENALINE, XYLONOR 2% SPECIAL and XYLONOR 3% NORADRENALINE:

SPC section 4.2

<Product> is indicated in adults and children. Special care has to be exercised when treating children below 4 years. The quantity to be injected should be determined by the age and weight of the child and the magnitude of the operation. The anaesthesia technique should be selected carefully. Painful anaesthesia techniques should be avoided. The behaviour of the child during treatment has to be monitored carefully.

The average dose to be used is in the range of 20 mg to 30 mg lidocaine hydrochloride per session. The dose in mg of lidocaine hydrochloride which can be administered in children may alternatively be calculated from the expression: child’s weight (in

kilograms) x 1.33.

Do not exceed the equivalent of 5 mg of lidocaine hydrochloride per kilogram of body weight.

For the Septodont topical anesthetic products

SPC section 4.1

"<Product>is indicated in children and adolescents aged 4 to 18 years of age.

4. Discussion on clinical aspects

Eight MAHs submitted a large number of completed paediatric studies for lidocaine, in accordance with Article 45 of the Regulation (EC) No 1901/2006, as amended on medicinal products for paediatric use. This procedure concerns only studies related to the use of lidocaine as a local anaesthetic, i.e. not as an antiarrhythmic medicinal product. In most of the products concerned, lidocaine is used in combination with other substances. Thus, this procedure concerns a variety of nationally approved products, formulations and different indications with large regional differences within EU.

Most MAHs stated initially that the submitted paediatric studies do not influence the benefit risk for their products and that there is no consequential regulatory action. Nevertheless, during the procedure a number of proposals to modify the SmPC have been made by the MAHs.

A general comment is that limited data is available in children. Since many products are combination products, it is considered difficult to provide general recommendations within the scope of this procedure. However, most MAHs should state in which age groups the product is indicated, specifying the age limits, e.g. '*X is indicated I <adults><neonates><infants><children><adolescents> <aged x to y <years, months>>*', in the SmPC section 4.1.

The MAHs should also update the PIL in accordance with the revisions in the SmPC, when relevant.

The studies related to MAHs specific products are discussed under each MAH:

Xylestesin-A (3M ESPE AG)

The product Xylestesin-A is a solution for injection containing Lidocaine hydrochloride 20 mg/ml and (R)-Epinephrine hydrochloride 0.015 mg/ml. The indication is Infiltration anesthesia and nerve-block in dentistry. The dosage should be individually determined from case to case depending on the method used and special characteristics of the particular case. Doses of 1-4 ml are sufficient for young persons over 15 years of age and adults. In children weighing about 20 - 30 kg, doses of 0.25 - 1 ml are sufficient; and in children weighing 30 - 45 kg, 0.5 - 2 ml. No more than 5 mg lidocaine per kg body weight should be injected in children.

No changes in the currently approved SmPC for Xylestesin-A were proposed.

The MAH submitted 11 publications from controlled clinical studies with lidocaine HCl 20 mg/ml and epinephrine HCl 0.015 mg/ml products used in dentistry. In the cover letter, the MAH of Xylestesin-A points out that the studies were not performed with this particular product since Xylestesin-A is a generic product.

Of the studies submitted, several had limitations in their study design (e.g. open-label) and in several of them efficacy of lidocaine in dental procedures in children or adolescents could not be confirmed. As pointed out by the MAH, several factors may influence the anaesthetic efficacy of local anaesthetics in dentistry, in adults as in children, e.g. administration techniques which may affect painfulness of administration. Even if the results are not very impressive, the data do not give any reason to change the current recommendations regarding the use of this product in children and adolescents. The safety data presented do not give rise to any new concerns in a paediatric population.

The maximum dosage for this product and similar products (Septodont/Xylonor) was discussed during the procedure. The maximum dose in dental use differed for these products, being 5 mg/kg for Xylestesin-A and 2.2 mg/kg for Septodont/Xylonor. Based on information submitted by the different MAHs and literature research by the Rapporteur it was concluded that the generally accepted recommended maximum dose for paediatric dental use reported in the literature is in the range of 4-5 mg/kg BW although the scientific basis for paediatric posology regarding dental injection lidocaine analgesia is not firm. There is no absolute contraindication for injectable analgesia in children below 4 years of age, even if it is mostly found not optimal.

SmPC modifications are proposed for sections 4.1 and 4.2. See recommendation.

EMLA (AstraZeneca)

EMLA is available as a cream and as a patch containing both lidocaine HCl and prilocaine HCl in a eutectic mixture. The approved indications (in Sweden and, presumably, most EU MS) for EMLA cream are: Local anaesthesia of the skin prior to needle insertion, and superficial surgical procedures; local anaesthesia of leg ulcers for cleaning and superficial surgical procedures such as removal of fibrin, pus and necrosis and local anaesthesia on genital mucosa.

EMLA medicated plaster is indicated for local anaesthesia of the skin prior to needle insertion, and superficial surgical procedures (in Sweden and, presumably, most EU MS).

The MAH did not provide the posology for EMLA in the clinical overview and a SmPC was not submitted. The posology for EMLA cream in children in the Swedish SmPC is 1 g per 10 cm² for use prior to needle insertion, and superficial surgical procedures. A thick layer of the cream should be applied under an occlusive bandage. The dose should not exceed 1 gram per 10 cm² and should be adjusted according to the application area and age. The posology for EMLA patch is 1 or several patches applied simultaneously for at least 1 hour in children aged 1-12 years. In children aged 3-12 months, 1 or at most 2 patches could be applied simultaneously for 1 hour. In children aged 0-3 months, 1 patch is the maximum daily dose and it should not be applied for more than 1 hour.

No explicit changes in the currently approved SmPCs for EMLA cream and patch were proposed by the MAH.

The MAH submitted a number of study reports (presumably) not previously submitted to all Member States. Most of the submitted studies, both those included in the "Clinical overview 2006" (describing previously submitted paediatric studies) and studies performed in other indications, were performed in the 1980s and the study reports were often brief and not up to current standards. Some studies were of double-blind, randomised, placebo-controlled design while others were open, un-controlled. In several but not all studies, EMLA was found to reduce pain during various procedures.

The data submitted by the MAH do not give rise to any new safety concerns except those already known and labelled for EMLA cream and patch, i.e. transient local skin reactions at the application site such as paleness, erythema and oedema, and in rare cases methaemoglobinaemia in children and allergic reactions (e.g. anaphylaxis).

In conclusion, the MAHs conclusion is endorsed by the Rapporteur, i.e. that the results of the clinical studies submitted within this procedure do not have any impact on the benefit/risk or paediatric prescribing information provided in the current SmPCs for EMLA cream and patch. However, references to use of EMLA during circumcision procedures should be removed since available data do not demonstrate adequate efficacy and section 4.1 should specify the age range for which the product is indicated.

Jelliproct (Grünentahl)

Grünentahl is the MAH for Jelliproct ointment and suppositories, registered in Germany since 1979. Jelliproct ointment contains 0,25 mg fluocinonide and 50,0 mg lidocaine hydrochloride per 1 g and Jelliproct suppositories contain 0,25 mg fluocinonide and 60,0 mg lidocaine per 1 suppository. The indications approved since August 2008 are as follows:

Jelliproct ointment: For short-term symptomatic treatment of inflammatory diseases in the area of the anus, especially haemorrhoids, proctitis and anal eczema. Application in connection with proctological interference.

Jelliproct suppositories: For short-term symptomatic treatment of inflammatory diseases in the area of the rectum, especially haemorrhoids and proctitis. Application in connection with proctological interference.

The SmPCs for both presentations did not include a specific paediatric posology or a lower age limit. Twice daily application is recommended for both ointment and suppositories and a duration of 1-2 weeks use should not be exceeded. No changes in the currently approved SmPC for Jelliproct were proposed.

The MAH submitted one multicentre, post-marketing, prospective, observational, non-interventional study (NIS) with the objective to investigate the efficacy, tolerability and safety of Jelliproct in the therapy of inflammatory diseases of the perianal region. The NIS study included 15 children and adolescents, and thus, provides limited information on the use of Jelliproct ointment and suppositories in the paediatric population. In this limited group, no AEs were reported and the tolerability was rated good or very good. The applicant's conclusion is that the efficacy/risk-ratio is considered positive for children and adolescents according to the data of the NIS. The number of patients in the paediatric population is too small to draw conclusions from, however, the data give no cause for concern in terms of safety.

Data from PSURs contained no information of concern for the paediatric population.

SmPC modifications are proposed in line with the SmPC guideline for section 4.1. See recommendation.

Dynexan (Kreussler Pharma)

Kreussler Pharma is the MAH for a medicinal product presented as a gel containing 2 % lidocaine hydrochloride as active pharmaceutical ingredient, Dynexan 2 %, gingival gel/paste. The medicinal product was registered first in Germany in 1976. In Germany, the indication and posology sections read as follows: "For temporary symptomatic treatment of pains at the oral mucosa, gingiva, and lips". "Adults: 4-8 times daily a pea-sized amount Dynexan Mundgel (this

corresponds of about 0.2 g gel or 4 mg lidocaine respectively). A total dosage of 40 mg lidocaine should not be exceeded. For children and infants dosage has to be done individually considering age and body weight (max. 4 times daily a pea-sized amount).”

In France, the marketing authorization for Dynexan 2 % was granted in 1999, initially for use of the medicinal product in adults only. Subsequently, in 2002 the AFSSAPS granted the use of the medicinal product for children with an age from 6 years on. In France, the indication and posology sections read as follows: “Symptomatic short-term treatment of painful lesions in the oral cavity. Local contact anaesthesia prior to instrumental examinations in odontology / stomatology.” “Adults: Application of 0.5 g cream, max. four times daily, corresponding to 40 mg lidocaine. Children from 6 to 15 years: Application of 0.5 g cream, max. four times daily, corresponding to 40 mg lidocaine.”

No changes in the currently approved SmPCs were proposed.

During the procedure, the MAH was asked to justify the indications for Dynexan gel and the use in children below the age of 6 years. It was concluded that there is no pivotal clinical trial available to support the use of Dynexan 2 % in small children but the MAH refers to well established use of the product. This is partly based on sales and prescription figures since the product is only allowed to be prescribed for children younger than 12 years of age but not for adults in Germany. PSUR data contained no information of concern for the paediatric population.

Dynexan gel is only approved and marketed in two MS, Germany and France, with somewhat different indications and age limits for use. In comments received by Germany, it is stated that the clinical usage of Dynexan is well established in children below the age of 6 years and there are no established safety concerns of note, for instance based on the latest PSUR.

Although the underlying data seem limited, it may not be relevant to limit the use only to an older age group in Germany for a product that has been on the market for many years with no obvious safety concerns. On the other hand, it may not be appropriate to suggest that the age limit of 6 years applied in France should be removed. This would likely necessitate submission of a type II variation for a change in the posology section of the SmPC in France.

Regarding other MS that do not have the product approved, the indications approved in DE and FR may not be considered appropriate, e.g. to use a lidocaine-containing product for treatment of conditions like teething pain.

SmPC modifications are proposed in line with the SmPC guideline for section 4.1. See recommendation.

Cathejell Lidocaine (Montavit)

Cathejell Lidocaine is a combination of lidocaine hydrochloride (20 mg/g) and chlorhexidine dihydrochloride (0.5 mg/g) available as a gel for intra-urethral instillation. The product is used for reduction of pain during catheterization and prevention of onset of urinary tract infections following transurethral procedures. However, the indication and the dose recommendation for children are not specifically described. No paediatric pharmacokinetic or paediatric pharmacodynamic studies with the combination product have been performed by the MAH. A Post Marketing Surveillance study, which was aimed at evaluation of efficacy and safety under routine therapeutic conditions, was submitted. Altogether the MAH submitted 37 published studies covering both active substances. Overall, the clinical effect of reducing pain during catheterization in infants and children seems weak on the basis of the submitted studies. There

are some data indicating a disinfecting effect of a lidocaine/chlorhexidine combination. It should be noted that Cathejell Lidocaine is not approved in Sweden and we don't have access to the data in the MAA file. Even if the results are not very impressive, the data do not probably give any reason to change the current recommendations in the countries where the product is approved regarding the use of this product in children and adolescents. The Rapporteur is aware of that the MAH already has submitted national variation applications to a number of the concerned member states and therefore the proposed modifications could already have been considered. SmPC modifications are proposed for sections 4.1, 4.2 and 4.3. See recommendation.

Orofar (Novartis)

Orofar is a combination of benzoxonium chloride and lidocaine hydrochloride, available as lozenges, gelsollets (both containing 1mg benzoxonium and 1 mg lidocaine), oromucosal spray (containing 2 mg benzoxonium and 1.5 mg lidocaine per ml) and oromucosal solution (containing 0.5 mg benzoxonium and 0.5 mg lidocaine per ml). The combination product is indicated for treatment of infections in the mouth and throat. The product is recommended for adults and for children and adolescents aged 4 years and above. No paediatric pharmacokinetic, paediatric pharmacodynamic or paediatric clinical efficacy studies have been performed with the benzoxonium/lidocaine combination product for oral use by the MAH. The MAH submitted 19 published studies, 9 internal reports (concerning benzoxonium only) and 3 PSURs (concerning the combination benzoxonium/lidocaine). The maximum recommended lidocaine doses for Orofar are 6 mg/day corresponding to 0.38 mg/kg (16 kg 4-year old child). Although no pharmacokinetic data is available for Orofar the anticipated plasma levels would clearly be below the plasma levels inducing toxic effects in a child. Orofar is not approved in Sweden. The combination product has been approved in some countries it seems on the basis of results from clinical efficacy and safety studies including paediatric studies performed with benzoxonium chloride at the maximum recommended daily dose, pharmacokinetic data for benzoxonium chloride in adults, published data on the pharmacokinetic of lidocaine in children and the established used for lidocaine as a local anaesthetic for the oropharyngeal cavity in children. Based on Orofar safety data, no new safety signals are detected in the pediatric patient population. SmPC modifications are proposed for sections 4.1, 4.4 and 4.8. See recommendation.

Strepsils +Plus (Reckitt Benckiser)

Strepsils +Plus is a combination of 0.6 mg amylmetacresol, 1.2 mg 2, 4-dichlorobenzyl alcohol, and 10mg lidocaine hydrochloride (2 mg in France) and available as lozenges. The combination product is indicated for the symptomatic relief of mouth and throat infections including severe sore throat and indicated for adults and children over the age of 12 years old. Efficacy studies have not been conducted in paediatric populations for the treatment of sore mouth other than some trials that included children aged 16 years submitted within the registration application. No unexpected effects on vital signs or following physical examination by investigating physicians have been reported after administration of Strepsils lozenges in clinical studies. Thus, no new safety concerns are identified in the adults, adolescents or children (from 12 years and older) in the most recent PSUR. SmPC modifications are proposed in line with the SmPC guideline for section 4.1. See recommendation.

Xylonor (Septodont)

Septodont is the manufacturer and the Marketing authorisation holder of several Lidocaine based products with an indication in anesthesia. There are two ranges: anaesthetic solutions for injection and topical anaesthesia.

The concerned products are listed in the table below:

Anaesthetic solution for injection		
Xylonor 3% Noradrenaline	Lidocaine 30 mg/ml Noradrenaline 0,004 mg/ml	Solution for injection
Xylonor 2% Noradrenaline	Lidocaine 20 mg/ml Noradrenaline 0,004 mg/ml	Solution for injection
Xylonor 2% Special	Lidocaine 20 mg/ml Adrenaline 0,02 mg/ml	Solution for injection
Lignospan Special	Lidocaine 20 mg/ml Adrenaline 0,0125 mg/ml	Solution for injection
Topical anaesthetic		
XOgel Child	Lidocaine 50 mg/g Cetrimide 1.5 mg/g	Gingival gel
XOgel Adult	Lidocaine 50 mg/g Cetrimide 1.5 mg/g	Gingival gel
Xylonor gel	Lidocaine 50 mg/g Cetrimide 1.5 mg/g	Gingival gel
Xylonor solution	Lidocaine 50 mg/ml Cetrimide 1.5 mg/ml	Solution for dental use
Xylonor pellets	Lidocaine 50 mg/ml Cetrimide 1.5 mg/ml	Impregnated cotton pellets for dental use
Xylonor Spray	Lidocaine 150 mg/g Cetrimide 1.5 mg/g	Solution
Xylonor Spray N	Lidocaine 150 mg/g	Solution

The MAH has submitted an Overview and the studies/articles which have not been described elsewhere related to the use of lidocaine as a local anaesthetic. The studies with a sufficient level of information were assessed. The pharmacokinetics of lidocaine in infants and children (between 3 months and 11 years old) reported by *Gunter (2002)* showed that the peak concentration (C_{max}) for lidocaine after typical clinical doses is below the accepted toxic threshold of 5 to 6 µg/ml. In general, C_{max}, time to C_{max} (t_{max}), volume of distribution at steady state (V_{dss}), clearance and half-life (t_{1/2}) values in children are comparable to the values seen in adults. It was further stated that lidocaine has a favourable toxicity profile and its uptake is decreased and duration of action increased with the addition of epinephrine. The maximum recommended single dose is 5 to 7 mg/kg (perhaps 8 to 10 mg/kg with epinephrine). In addition the MAH submitted three PSURs. For lidocaine, from 2002- 2009, three cases were reported for children whereas more than 3 million of units were sold. No new specific areas of pharmacovigilance interest were identified which needed to be included in the SmPC. The MAH also concluded that the occurrence of gingival ulceration, blister and sloughing will be continued to be closely monitored for the lidocaine/cetrimide products. Overall it can be concluded that the efficacy and safety of these products are well established.

The MAH has proposed to amend SmPC section 4.2 for the XYLONOR SPECIAL and XYLONOR NORADRENALINE with the inclusion of a new table. The maximum dose in dental use was evaluated also for Xylestesin-A and it was noted that there was a difference in the maximum dose proposed; i.e., maximum dose in 5 mg/kg for Xylestesin-A and 2.2 mg/kg for Septodont/Xylonor. Based on the information submitted by the different MAHs and the literature research by the Rapporteur it can be concluded that the scientific basis for paediatric posology regarding dental injection lidocaine analgesia is not firm. The MAH Septodont has suggested 2.0 mg/kg BW of lidocaine as a conservative dose. The Rapporteur is of the opinion (after studying available, admittedly limited, data) that a more appropriate conservative dose is in the vicinity of 1.33 mg/kg BW as earlier suggested by the MAH. However, the maximum recommended dose of 2.2 mg/kg BW is probably a calculation mistake, maybe due to a mix-up between kg and lb in

the initial marketing approval procedure. The generally accepted recommended maximum dose for paediatric dental use reported in the literature is in the range of 4-5 mg/kg BW. SmPC modifications are proposed for section 4.1 and 4.2. See recommendation below.

V. MEMBER STATES OVERALL CONCLUSION AND RECOMMENDATION

➤ Overall conclusion

Eight MAHs submitted a large number of completed paediatric studies for lidocaine. It should be noted that this procedure concerns only studies related to the use of lidocaine as a local anaesthetic. In most of the products concerned, lidocaine is used in combination with other substances. Thus, this procedure concerns a variety of nationally approved products, formulations and different indications with large regional differences within EU.

Most MAHs stated initially that the submitted paediatric studies do not influence the benefit risk for their products and that there is no consequential regulatory action. Nevertheless during the procedure a number of proposals to modify the SmPC have been made by the MAHs, clinical data was assessed during the procedure and SmPC modifications were proposed. See recommendation below.

A general comment is that limited data is available in children. Since many products are combination products, it is considered difficult to provide general recommendations within the scope of this procedure. However, most MAHs should state in which age groups the product is indicated, specifying the age limits, e.g. '*X is indicated in <adults><neonates><infants><children><adolescents> <aged x to y <years, months>>*', in the SmPC, section 4.1.

The MAH should also update the PIL in accordance with the revisions in the SmPC, when relevant.

➤ Recommendation

Type IB variation to be requested from the MAH by 1st of May 2013.

Xylestesin-A

The following SmPC modifications are proposed:

Section 4.1

It should be stated in which age groups the product is indicated, specifying the age limits, e.g. ***X is indicated in <adults><neonates><infants><children> <adolescents> <aged x to y <years, months>***

Section 4.2

<Product> is indicated in adults and children. Special care has to be exercised when treating children below 4 years. The quantity to be injected should be determined by the

age and weight of the child and the magnitude of the operation. The anaesthesia technique should be selected carefully. Painful anaesthesia techniques should be avoided. The behaviour of the child during treatment has to be monitored carefully.

The average dose to be used is in the range of 20 mg to 30 mg lidocaine hydrochloride per session. The dose in mg of lidocaine hydrochloride which can be administered in children may alternatively be calculated from the expression: child's weight (in kilograms) x 1.33.

Do not exceed the equivalent of 5 mg of lidocaine hydrochloride per kilogram of body weight.

EMLA cream

The following SmPC modifications are proposed:

Section 4.1

It should be stated in which age groups the product is indicated, specifying the age limits, e.g. ***X is indicated in <adults><neonates><infants><children> <adolescents> <aged x to y <years, months>>.***

Other sections

References to the use of EMLA for male circumcision should be removed.

Jelliproct

The following SmPC modifications are proposed:

Section 4.1

It should be stated in which age groups the product is indicated, specifying the age limits, e.g. ***X is indicated in <adults><neonates><infants><children> <adolescents> <aged x to y <years, months>>.***

Dynexan

The following SmPC modifications are proposed:

Section 4.1

It should be stated in which age groups the product is indicated, specifying the age limits, e.g. ***X is indicated in <adults><neonates><infants><children> <adolescents> <aged x to y <years, months>>.***

Cathejell Lidocaine (Pharmazeutische Fabrik Montavit Ges.m.b.H) gel, lidocaine 2%

The Rapporteur is aware of that the MAH already has submitted national variation applications to a number of the concerned member states and therefore the proposed modifications could already have been considered.

The following SPC modifications are proposed:

Section 4.1

It should be stated in which age groups the product is indicated, specifying the age limits, e.g. ***X is indicated in <adults><neonates><infants><children> <adolescents> <aged x to y <years, months>>.***

Section 4.2

The following should be included:

“In women, children (2-12 years) and adolescents (under 18 years) the effect of Cathejell with lidocaine is not so well demonstrated and therefore the need to use it should be assessed by the doctor. Specific dosage recommendations cannot be given for these groups of patients, but as a general rule, the amount of gel instilled is adapted to the individual anatomical conditions of the urethra.

The systemic absorption of lidocaine can be increased in children and caution is accordingly required. In general, the maximum dose in children aged 2 to 12 years of 2.9 mg/kg lidocaine hydrochloride should not be exceeded.

Cathejell with lidocaine must not be used in children under 2 years (see section 4.3).”

Section 4.3

Relevant text should be included regarding children.

Orofar (Novartis Health care) lozenge, lidocaine 1 mg:

The following SmPC modifications are proposed:

Section 4.1

The following should be included:

“Orofar is indicated in children and adolescents aged 4 to 18 years of age”_alternatively ***“Orofar is indicated in children and adolescents aged 6 to 18 years of age”*** depending on the already approved age range in children in the concerned member state.

Section 4.4

The following should be included:

“Pediatric population:”

“Orofar should not be used in children aged less than 4 years.”_alternatively ***“Orofar should not be used in children aged less than 6 years.”*** depending on the already approved age range in children in the concerned member state.

Section 4.8

The following should be included:

“Pediatric population:

Frequency type and severity of adverse reactions in children are expected to be same as in adults.”

Strepsils +Plus (Reckitt Benckiser) lozenge, lidocaine 10 mg

The following SmPC modifications are proposed:

Section 4.1

The following should be included:

“Strepsils Plus is indicated in children and adolescence aged 12 to 18 years of age”.

Xylonor (Septodont)

The following SmPC modifications are proposed:

LIGNOSPAN 2% SPECIAL, XYLONOR 2% NORADRENALINE, XYLONOR 2% SPECIAL and XYLONOR 3% NORADRENALINE:

Section 4.2

<Product> is indicated in adults and children. Special care has to be exercised when treating children below 4 years. The quantity to be injected should be determined by the age and weight of the child and the magnitude of the operation. The anaesthesia technique should be selected carefully. Painful anaesthesia techniques should be avoided. The behaviour of the child during treatment has to be monitored carefully.

The average dose to be used is in the range of 20 mg to 30 mg lidocaine hydrochloride per session. The dose in mg of lidocaine hydrochloride which can be administered in children may alternatively be calculated from the expression: child's weight (in kilograms) x 1.33.

Do not exceed the equivalent of 5 mg of lidocaine hydrochloride per kilogram of body weight.

For the Septodont topical anesthetic products

Section 4.1

“<Product> is indicated in children and adolescents aged 4 to 18 years of age.

VI. LIST OF MEDICINAL PRODUCTS AND MARKETING AUTHORISATION HOLDERS INVOLVED

MAH	Name of the medicinal product	Strength	Pharmaceutical form
3M ESPE AG, ESPE Platz, D-82229 Seefeld	Neo-Xylestesin	20 mg/ml + 12 µg/ml	solution for injection
3M ESPE AG, ESPE Platz, D-82229 Seefeld	Xylestesin A	20 mg/ml + 12 µg/ml	solution for injection
AstraZeneca Ltd UK	EMLA	25 mg/g + 25 mg/g	cream and medicated plaster
Grünenthal GmbH, Zieglerstr. 6, 52078 Aachen	Jelliproct	0.25 mg/50 mg per g	ointment
Grünenthal GmbH, Zieglerstr. 6, 52078 Aachen	Jelliproct	0.25 mg/60 mg per g	suppository

Chemische Fabrik Kreussler & Co. GmbH	Dynexan 2% crème buccale	20 mg/g	cream
Chemische Fabrik Kreussler & Co. GmbH	Dynexan Mundgel	20 mg / g	gel
Pharmazeutische Fabrik Montavit GmbH	Cathejell mit Lidocain - anaesthesierendes Gel (sterile Einmalabgabeform)	2 % 0.05 %	urethral gel
Pharmazeutische Fabrik Montavit GmbH	Cathejell avec lidocaïne - gel anesthésiant	2 % 0.05 %	urethral gel
Pharmazeutische Fabrik Montavit GmbH	Cathejell with Lidocaine	2 % 0.05 %	urethral gel
Pharmazeutische Fabrik Montavit GmbH	Cathejell with lidocaine gel	2 % 0.05 %	gel for intra-urethral instillation
Pharmazeutische Fabrik Montavit GmbH	Cathejell Lidocain	2 % 0.05 %	catheter lubricant gel
Pharmazeutische Fabrik Montavit GmbH	Urogliss	2 % 0.05 %	urethral gel
Pharmazeutische Fabrik Montavit GmbH	Cathejell	2 % 0.05 %	gele uretral
Pharmazeutische Fabrik Montavit GmbH	Cathejell cu Lidocaină	2 % 0.05 %	urethral gel
Novartis Hungaria Kft. Consumer Health	OROFAR LIDOCAINE 1+1MG GELSOLETS	1+1mg	gelsolet
Novartis Consumer Health GmbH, 81366 München	Orofar-L Gurgellösung	0,05 g, 0,05 g/ 100 ml	solution
Novartis Consumer Health GmbH, 81366 München	Orofar-L Mundspray	0,20 g, 0,15 g/ 100 ml	solution
Novartis Consumer Health GmbH, 81366 München	Orofar-L Tabletten	1,0 mg, 1,0 mg	tablet
Novartis Consumer Health GmbH, 81366 München	Orofar-L Weichgelatine kapseln	1,0 mg, 1,0 mg	capsules
Reckitt Benckiser Healthcare S.A. TABLA 1	Strepsils con lidocaína pastillas para chupar	0.6 mg AMC; 1.2 mg DCBA; Lidocaine 2mg	lozenge
SEPTODONT	XYLONOR 2 POUR CENT NORADRENALINE pour une cartouche de 1,8 ml	38,412 mg 36,00 mg 0,144 mg 0,072 mg	solution injectable à usage dentaire
SEPTODONT	XYLONOR 2 POUR CENT	38,4120 mg	solution injectable

	SPECIAL pour une cartouche de 1,8 m	36,0000 mg 0,0410 mg 0,0225 mg	à usage dentaire
SEPTODONT	XYLONOR 3 POUR CENT NORADRENALINE pour une cartouche de 1,8 ml	57,618 mg 54,00 mg 0,144 mg 0,072 mg	solution injectable à usage dentaire
SEPTODONT	XYLONOR SPRAY	15 %+ 0.15%	metered aerosol