

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

**Mepivastesin 30mg/ml (BE,BG,DE,LT,RO)
Scandonest 30mg/ml (DK)
Scandonest 3% SVC (PL)
Scandonest 3% ohne Vasokonstriktor Zylinderampullen
(AT)**

INN: Mepivacaine

AT/W/0002/pdWS/001

Rapporteur:	AT
Finalisation procedure (day 120):	13.10.2010
Date of finalisation of PAR	05.11.2010

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product(s):	See section VII
INN (or common name) of the active substance(s):	mepivacaine
MAH (s):	See section VII
Pharmaco-therapeutic group (ATC Code):	N01BB03
Pharmaceutical form(s) and strength(s):	30mg/ml solution for injection

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I. EXECUTIVE SUMMARY

Legal background

Art. 45 of Reg. 1901/2006

By 26 January 2008, any paediatric studies already completed, by the date of entry into force, in respect of products authorised in the Community shall be submitted by the marketing authorisation holder for assessment to the competent authority.

The competent authority may update the Summary of Product Characteristics and Package Leaflet, and may vary the marketing authorisation accordingly. Competent authorities shall exchange information regarding the studies submitted and, as appropriate, their implications for any marketing authorisations concerned.

The EMA shall coordinate the exchange of information.

Mepivacaine

For the worksharing procedure concerning Art.45 of Reg. No 1901/2006, as amended, Austria has been appointed as rapporteur for mepivacaine.

Three marketing authorisation holders (SEPTODONT, FR, 3M ESPE, DE and N.V.Denta S.A., BE) has submitted eight studies to support the posology of mepivacaine 30mg/ml for children given in the SmPC for the therapeutic indications: “Infiltration anaesthesia and nerve-block in dentistry. Mepivastesin is indicated for simple extractions as well as cavity and stump preparations. Mepivastesin is especially suitable for patients to whom vasoconstricting additives are contraindicated”.

From these studies in only 4 studies mepivacaine 3% has been used. Neither of these studies provided adequate data to support the claimed posology for children in the SmPC.

Neither the studies using 2% mepivacaine with vasoconstrictor corroborated the claimed posology.

Both MA Holder 3M ESPE and Septodont opposed the Assessor’s initial recommendation by scientific argumentation and documentation which has been accepted by the assessor and resulted in an alternative wording in 4.2. and 4.3. of the SmPC.

II. RECOMMENDATION

The claimed posology for mepivacaine 30mg/ml in children as a local anaesthetic in dentistry should be changed as follows:

Proposed changes in the SmPC:

4.2. The present text should be deleted:

In children weighing about 20-30kg, doses of 0.25-1ml are sufficient; and in children weighing 30-45kg, 0.5-2ml.

Children:

The quantity to be injected should be determined by the age and weight of the child and the magnitude of the operation. Do not exceed the equivalent of 4mg mepivacaine/kg (0.133ml Mepivastesin/kg) of body weight.

and replaced by:

4.2. Children:

Children from 4 years of age (ca.20kg body weight) and older (see 4.3.)

Recommended therapeutic dose:

The quantity to be injected should be determined by the age and weight of the child and the magnitude of the operation. The average dosage is 0.75mg/kg=0.025ml of mepivacaine solution per kg body weight.

Maximum recommended dosage:

Do not exceed the equivalent of 3mg mepivacaine/kg (0.1ml mepivacaine/kg) of body weight.

4.3. to be added

- children below 4 years of age (ca.20kg body weight).

A Type IB variation to be requested from the MAH by day 180 of the procedure.

III. INTRODUCTION

Three MAHs submitted 8 completed paediatric studies for mepivacaine, in accordance with Article 45 of the Regulation (EC)No 1901/2006, as amended on medicinal products for paediatric use.

A short critical expert overview has also been provided.

The MAH stated that the submitted paediatric studies do not influence the benefit/risk for Mepivastesin 30mg/ml and that there is no consequential regulatory action.

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

IV. SCIENTIFIC DISCUSSION

IV.1 Information on the pharmaceutical formulation used in the clinical studies

Mepivacaine 2% with 1:20.000 levonorfedrin (Winthrop Laboratories South Africa and Astra Pharmaceuticals)

Carbocaine (Mepivacaine 2% with epinephrine 1:200.000, Cooke-Waite, New York)

Mepivacaine 2% (without further data)

Polocaine with Levonorfedrin (Mepivacaine 2% with 1:20.000 levonorfedrin)

Polocaine (3% mepivacaine without vasoconstrictor)

3% mepivacaine (Winthrop Laboratories South Africa)

Carbocaine 3% (3% mepivacaine without vasoconstrictor)

Scandonest cartridge 3% (3% mepivacaine without vasoconstrictor, Nippon Shika Yakuhin Kabushiki Kaisha)

No specific paediatric formulation exists.

IV.2 Non-clinical aspects

1. Introduction

No non-clinical studies were submitted

2. Non clinical studies

None

3. Discussion on non clinical aspects

Assessor's comment: Accepted as not required.
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IV.3 Clinical aspects

1. Introduction

The MAH Septodont submitted 3 reports = publications for:

- Clinical evaluation of mepivacaine and lidocaine.”
*Bradley DJ., Martin ND.,
Australian Dental Journal, December 1969:377-81.*
- Toxicity of local anaesthetics in infants and children.
*Berde CB.,
Journal of Paediatrics 1993; 122:S14-S20.*
- Clinical study on the efficacy of the Scandonest cartridge 3% (1.8ml) in paediatric dentistry.
*T.Tokiyasu, T.Akasaka, T.Komatsu, S.Watanabe.
Oral Therapeutics and Pharmacology Vol. 24, No.1, Supplement, pp.13-19 (issued on 1 April 2005).*

The MAH 3M ESPE submitted 6 reports = publications for:

- A double blind study comparing the local anaesthetic efficacy of 3 per cent Mepivacaine with 2 per cent Mepivacaine containing a vasoconstrictor.
*Aronson M. and Bomzon L.
Journal of the Dental Association of South Africa, 1981, 36, (9) 611-613.*
- Serum mepivacaine concentrations after intraoral injection in young children.
*Chin, K.L., Yagiela, J.A., Quinn, C.L. et al.
Journal Calif. Dent. Assoc. 2003, 31 (10) 757-764.*
- Bilateral versus unilateral mandibular block anaesthesia in a paediatric population.
*College, C., Feigal, R., Wandera, A. et al.
Paediatric. Dent. 2000, 22 (6) 453-457*

- Evaluation of mandibular infiltration versus block anaesthesia in paediatric dentistry.
Sharaf,A.A.
ASDC. J. Dent. Child. 1997. 64 (4) 276-281.
- The effectiveness of infiltration anaesthesia in the mandibular primary molar region.
Wright, G.Z., Weinberger, S.J., Marti, R. et al.
Paediatric Dent. 1991, 13 (5) 278-283.
- Clinical evaluation of mepivacaine and lidocaine.”
Bradley DJ.,Martin ND.,
Australian Dental Journal, December 1969:377-81. (Already submitted by Septodont).

The MAH 3M ESPE submitted an expert overview for their submitted publications.

2. Clinical studies

1. STUDIES FROM SEPTODONT

1) Bradley DJ.,Martin ND

Description

Clinical evaluation of mepivacaine and lidocaine.
Australian Dental Journal, 1969, 14 (6):377-81.

Methods

- Objective(s)
To compare the local analgesic properties of mepivacaine hydrochloride (Carbocaine) 3 percent without vasoconstrictor and of lidocaine hydrochloride (Xylocaine) 2 percent with 1:100.000 epinephrine in children’s dentistry.
- Study design
Randomised, double-blind study
- Study population /Sample size
254 children, aged 5-14 years. No significant differences in the distribution of boys and girls, median ages or median weights (in lbs.!) between the appropriate treatment groups.
- Treatments
Infiltration or mandibular injection of 0.8ml to 3.6ml solution Carbocaine 3% or Xylocaine 2% (with 1:100.000 epinephrine).
- Outcomes/endpoints
Median onset time (sec.), median duration of numbness (hours, minutes), grade of anaesthesia (A: complete elimination of pain, B: injection not repeated but some pain, C: reinjection necessary).
- Statistical Methods
Not specified, only comparison between anaesthetics with two types of injection, infiltrative and block (mandibular).

Results

- Recruitment/ Number analysed
254 children: 131 boys, 123 girls. 254 analysed.
- Baseline data

TABLE 1
Distribution of 131 boys and 123 girls receiving **Xylocaine 2 per cent (epinephrine 1 : 100,000)** and **Carbocaine 3 per cent anaesthetic injections**

	Xylocaine 2 per cent (epinephrine 1 : 100,000)		Carbocaine 3 per cent	
	Infiltrative	Mandibular	Infiltrative	Mandibular
Number of boys	44 (54)	30 (54)	30 (45)	27 (54)
Number of girls	38 (46)	26 (46)	36 (55)	23 (46)
Median age (yrs.)	7	7	7	7
90% range	5-13	5-14	6-12	5-11
Median weight (lb.)	60	56	60	56
90% range	42-100	42-113	42-100	38-111
Emotional state				
Calm	50 (63)	30 (58)	43 (66)	27 (55)
Nervous	29 (37)	22 (42)	22 (34)	22 (45)
Not recorded	3	4	1	1
Total number of children	82	56	66	50

Percentage figures in brackets.

138

126

- Efficacy results

TABLE 3
Anaesthetic reaction to infiltration or mandibular injection of 0.8-3.6 ml solution in 254 children

	Xylocaine 2 per cent (epinephrine 1 : 100,000)		Carbocaine 3 per cent	
	Infiltrative	Mandibular	Infiltrative	Mandibular
Median onset time (sec.)	55"	40"	50"	45"
90% range (min. sec.)	6"-3' 50"	10"-3'	10"-4'	5'-4' 10"
Median duration of numbness (hr. min.)	2 19*	2 58'	1 54*	3 21'
90% range (hr. min.)	37'-4 14'	26'-3 58'	1 04'-5 09'	1 05'-4 37'
Grade of anaesthesia				
A—complete elimination of pain	61 (76)	39 (71)†	45 (70)	43 (88)†
B—injection not repeated but some pain	12 (15)	11 (20)	10 (16)	5 (10)
C—re-injection necessary	7 (9)	5 (9)	9 (14)	1 (2)
Not recorded	2	1	2	1
Total number of children	82	56	66	50

* Significant difference between medians $0.01 < P < 0.05$; $\chi^2 = 5.94$.

† Significantly more Grade A with **Carbocaine** $P = 0.05$; $\chi^2 = 4.41$.

Percentage figures in brackets.

- Safety results

TABLE 4
Systemic reactions to the anaesthetic injection in 254 children

	Xylocaine 2 per cent (epinephrine 1 : 100,000)		Carbocaine 3 per cent	
	Infiltrative	Mandibular	Infiltrative	Mandibular
Number of children	82	56	66	50
Degree of bleeding				
None	58 (81)	35 (80)	40 (68)	33 (70)
Slight	10 (14)	7 (16)	16 (27)	7 (15)
Moderate	4 (5)	2 (4)	3 (5)	7 (15)
Excessive	—	—	—	—
Not recorded	10	12	7	3
Systemic reactions				
None	74 (95)	53 (96)	52 (90)	47 (94)
Nausea	2 ⁽¹⁾	1	2	1 ⁽²⁾
Faintness	2	1 ⁽²⁾	2	—
Palpitation	—	—	—	1
Perspiration	—	—	1	1 ⁽¹⁾
Irritation	—	—	1	—
Not recorded	4	1	8	—
Postoperative reactions				
None	52 (98)	40 (100)	38 (90)	34 (94)
Soreness injection site	1	—	1	2
Swelling injection site	—	—	3	—
Not recorded	29	16	24	14

Percentage figures in brackets.

Additional symptoms: ⁽¹⁾ One with stomach ache, faintness; ⁽²⁾ Perspiration, rapid pulse;
⁽³⁾ Tremors; ⁽⁴⁾ Faintness.

Summary

Mepivacaine hydrochloride (Carbocaine) 3% without any vasoconstrictor and lidocaine hydrochloride (Xylocaine) 2% with 1:100,000 epinephrine were compared for local anaesthetic effect for routine procedures in children's dentistry. The study was double-blind on 254 children. Both solutions provided rapid and satisfactory anaesthesia. Neither was notably superior to the other except that mepivacaine hydrochloride 3% did offer the advantages of being well tolerated and of providing satisfactory anaesthesia of considerably shorter duration of effect.

Assessors comments: Efficacy and tolerance of 0.8ml-3.6ml of Carbocaine 3% (mepivacaine 3%) without vasoconstrictor in 66 children with infiltrative and 50 children with mandibular injection (aged 5-12 years) has been demonstrated.

However, no differentiation in children weighing 20-30kg and 30-45kg, respectively according to 4.2. of the SmPC has been described. An age range of 5-12years and body weight in lbs. (38-111 lbs.) has been given only.

Therefore the posology for children in 4.2. of the SmPC can not be verified from the data of this publication.

2) Berde CB.

Description

Toxicity of local anaesthetics in infants and children
Journal of Paediatrics 1993; 122:S14-S20.

Objectives

The purpose of this article is to describe the toxicities (systemic toxic reactions affecting the heart and brain) and provide recommendations for their prevention and treatment in paediatrics.

Summary

Local anaesthetics are extremely useful for providing anaesthesia and analgesia for infants and children of all ages. Despite the toxicity issues raised here, the overall safety record of local anaesthetic use in paediatrics has been very good, and local anaesthetic administration within safe guidelines should be encouraged. In the great majority of cases toxic reactions have been associated with either inadvertent intravascular injection or unintentional overdosage by physicians who did not adequately consider issues related to systemic drug uptake, distribution or clearance. Unlike opioids, which can be titrated according to clinical signs to a wide range of doses, local anaesthetic administration must be strictly limited by the numbers. Paediatricians, surgeons, emergency room physicians and anaesthesiologists need to be informed regarding limits for the administration of local anaesthetics and management of toxic reactions.

Assessors comments: The well known toxicities of local anaesthetics in general has been described only without data for posology in children

3) *T.Tokiyasu, T.Akasaka, T.Komatsu, S.Watanabe.*

Description

Clinical study on the efficacy of the Scandonest cartridge 3% (1.8ml) in paediatric dentistry.
Oral Therapeutics and Pharmacology Vol. 24, No.1, Supplement, pp.13-19 (issued on 1 April 2005).

Methods

- Objective(s)
3% mepivacaine hydrochloride (Scandonest cartridge 3% from Nippon Shika Yakuhin Kabushiki Kaisha) was used to clinically evaluate its usefulness in paediatric dentistry.
- Study design
Open study.
- Treatments
Scandonest cartridge 3% (mepivacaine 3%), 1.36±0.22ml (0.9ml -1.8ml) normal infiltration anaesthesia administered through periosteal injection.
- Outcomes/endpoints
Efficacy: Very effective: There was no pain at all during surgery/treatment
Effective: There was some discomfort during surgery/treatment, but there was no particular problem (no additional administration). Somewhat effective. There was pain during treatment, and surgery/treatment became impossible. Procedure was completed after additional administration.
Ineffective: There was pain during treatment, and surgery/treatment became impossible. Additional preparation was administered, but it was not possible to complete the treatment with three cartridges.
Effectiveness rate (%): sum of very effective + effective.
- Statistical Methods

None.

Results

- Recruitment/ Number analysed
59 paediatric patients (28 males, 31 females) with no systemic health issues. Age range: 2 years 9 months to 15 years 3 months.
- Baseline data
Not applicable (n.a.)
- Efficacy results

Table 2. Dose administered for each group, total treatment time and percentage of effective anaesthesia

All treatments	Average dose (ml) 1.36 ± 0.22	Average treatment time (minutes) 26.1 ± 6.8	Effectiveness rate (%) 90
Crown restoration treatment group	1.39 ± 0.19	26.3 ± 5.9	98.3
Pulp treatment group	1.46 ± 0.20	30.6 ± 6.2	41.7
Tooth extraction treatment group	1.05 ± 0.23	19.0 ± 8.1	100

Crown restoration treatment group: 73.7% of patients.

Pulp treatment group: 15.0% of patients.

Tooth extraction group: 11.3% of patients.

Table 3. Cases where the effect of anaesthesia was insufficient

	Age	Sex	Site	Treatment	Initial dose	Total treatment time	Anaesthetic effect
1	4 y 2 m	F	D	Vital pulpectomy	1.35 ml	21 min	somewhat effective
2	4 y 2 m	F	E	Tooth extraction	1.8 ml	31.5 min	somewhat effective
3	4 y 3 m	M	D	Tooth extraction	1.35 ml	26 min	somewhat effective
4	4 y 4 m	F	E	Vital pulpectomy	1.35 ml	25 min	somewhat effective
5	4 y 4 m	M	E	Vital pulpectomy	1.8 ml	41 min	somewhat effective
6	6 y 6 m	F	DE	Vital pulpectomy	1.35 ml	41 min	somewhat effective
7	6 y 10 m	F	E	Resin restoration	1.35 ml	24 min	somewhat effective
8	7 y 7 m	M	D	Vital pulpectomy	1.35 ml	36 min	somewhat effective

- Safety results

No adverse reaction including localised adverse reaction and systemic adverse reaction was observed in any case.

Summary

Usefulness of Scandonest ® cartridge 3% for paediatric dentistry was assessed in 59 paediatric cases (28 males, 31 females). 73.7% of treatments were crown restoration and the rate of effectiveness in those treatments was 98.3%. Because it does not contain preservatives or antioxidant, and because its duration of action is relatively short, Scandonest ® is useful as one of the choices of local anaesthetic preparation

for crown restoration treatment. It was deemed to be worth considering as the primary choice of local anaesthetic preparation.

Assessors comments: Efficacy and safety of 1.36±0.22ml (0.9-1.8ml) of Scandonest cartridge 3% (mepivacaine 3%) in 59 paediatric patients (age range: 2 years 9 months to 15 years 3 months) with infiltrative anaesthesia has been demonstrated in the crown restoration treatment group only.

In the pulp treatment group effectiveness rate was only 41.7%.

In the tooth extraction group effectiveness rate was 100%, which is in contradiction with the two patients, where the anaesthetic effect was only somewhat effective. However, this rating was not included in the effectiveness rating (very effective +effective). Therefore the effectiveness rate of 100% is questionable.

No differentiation in children weighing 20-30kg and 30-45kg, respectively according to 4.2.of the SmPC has been described. An age range of 2 years 9 months to 15 years 3 months has been given only without data for body weight.

Therefore the posology for children in 4.2. of the SmPC can not be verified from the data of this study.

2. STUDIES FROM 3M ESPE

1) Aronson M. and Bomzon L.

Description

A double blind study comparing the local anaesthetic efficacy of 3 per cent Mepivacaine with 2 per cent Mepivacaine containing a vasoconstrictor.

Journal of the Dental Association of South Africa, 1981, 36, (9) 611-613.

Methods

- Objective(s)
To determine if there were any clinical differences in the local anaesthetic effect between a 3 per cent mepivacaine solution and a 2 per cent solution with levonorfedrin.
- Study design
Comparative, double-blind study, injection of 1ml on each side over 10 seconds for bilateral mandibular nerve block. 4 groups of patients: Group A (n=14): those that received 3% mepivacaine on each side
Group B (n=13). those that received 2% mepivacaine with the vasoconstrictor on each side
Group C (n=11): those that received 3% mepivacaine on the right side and 2% mepivacaine with vasoconstrictor on the left side.
Group D (n=12): those that received 2% mepivacaine with vasoconstrictor on the right side and 3% mepivacaine on the left side.
- Outcomes/endpoints
Onset time (mins) of anaesthesia, duration (mins) of anaesthesia, effectiveness of anaesthesia (scale 0-4) with 4 giving the ideal result.
- Statistical methods
Student's t-test comparing left and right side responses for each group. A p-value < 0.05 was considered to be statistically significant.

Results

- Recruitment/ Number analysed
50 patients, male and female patients over 16 years of age.

- Baseline data
N/A.
- Efficacy results
There were no significant differences between right and left side and between the 4 groups, respectively.

Table 1. Onset times, duration and effectiveness of the two local anaesthetics. (see text for the definition of each group.)

		Onset Time (mins)		Duration (hours)		Effectiveness			
						Patient		Operator	
		Right	Left	Right	Left	Right	Left	Right	Left
Group A (n = 14)	\bar{x}	4,0	4,0	2,28	2,23	3,4	3,4	3,3	3,1
	s.e.m.	0,4	0,5	0,26	0,27	0,2	0,2	0,3	0,3
Group B (n = 13)	\bar{x}	4,6	4,4	2,08	2,12	3,2	3,3	3,2	3,2
	s.e.m.	0,5	0,4	0,24	0,21	0,3	0,3	0,3	0,3
Group C (n = 11)	\bar{x}	4,2	3,9	2,82	2,64	3,5	3,5	3,5	3,5
	s.e.m.	0,6	0,5	0,27	0,32	0,3	0,2	0,3	0,2
Group D (n = 12)	\bar{x}	4,6	4,6	2,17	2,38	3,1	3,5	3,1	3,4
	s.e.m.	0,6	0,4	0,24	0,23	0,4	0,2	0,4	0,3

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- Safety results
Not reported.

Summary

This double blind study compares the local anaesthetic effects in 50 patients of a 3% mepivacaine solution with a 2% mepivacaine solution containing levonorfedrin as the vasoconstrictor. The comparisons were made between onset time and duration and effectiveness of each local anaesthetic solution. The results of this study indicate that there were no significant clinical differences between the 2 solutions.

Assessors comments: No significant difference in the efficacy of 1ml mepivacaine 3% vs. 1ml mepivacaine 2% containing a vasoconstrictor in 50 patients over 16 years of age has been revealed. Safety data are missing. No differentiation in children weighing 20-30kg and 30-45kg, respectively according to 4.2. of the SmPC has been described as patients with an age range over 16 years has been included only without data for body weight. Therefore the posology for children in 4.2. of the SmPC can not be verified from the data of this study.

2) *Chin, K.L., Yagiela, J.A., Quinn, C.L. et al.*

Description

Serum mepivacaine concentrations after intraoral injection in young children.
Journal Calif. Dent. Assoc. 2003, 31 (10) 757-764.

Methods

- Objective(s)

To help verify maximum dosage limits for mepivacaine in children and ultimately increase the safety of local anaesthetics in dentistry.

- Study design

Patients randomised to receive intraoral injection of either $2.96 \pm 1.13 \text{ mg/kg}$ 2% mepivacaine with 1:20,000 levonordefrin or $4.42 \pm 1.38 \text{ mg/kg}$ 3% mepivacaine without vasoconstrictor. Patients received also light general anaesthesia.

- Outcomes/endpoints

Serum mepivacaine concentrations by gas-liquid chromatography.

- Statistical methods

An analysis of variance with repeated measures was used to compare the serum concentrations of mepivacaine for the two drug treatments over time. Student's t-test was used to compare patient characteristics, mepivacaine dosages and volumes, peak serum concentrations, and times to peak concentrations. Linear regression forced through the origin was used to correlate the injected dose with the peak concentration of mepivacaine.

Results

- Recruitment/ Number analysed

36 children, ages of 2 to 5 years.

- Baseline data

	3% mepivacaine	2% mepivacaine + levonordefrin
Age (mo)	$47 \pm 13^*$	$47 \pm 12^*$
Weight (kg)	$16.7 \pm 3.7^*$	$18.1 \pm 5.0^*$
Race (His/Cauc/AfAm)	8/9/3†	

*Mean \pm SD
†Numbers of Hispanic/Caucasian/African American children enrolled

- Efficacy results

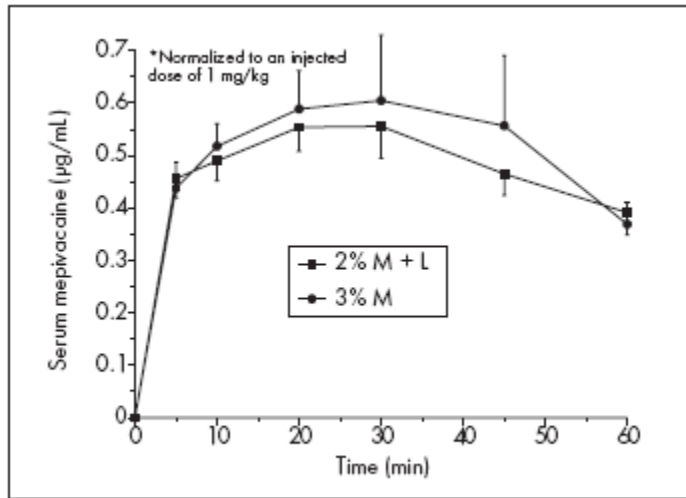


Figure 3. Serum mepivacaine concentrations normalized to an injected dose of 1 mg/kg. Bars indicate the standard errors. M = mepivacaine; L = levonordefrin

Mean serum concentrations, normalised to a dose of 1mg/kg body weight, reached a peak of 0.67 ± 0.42 ug/ml (mean \pm SD) after 3% mepivacaine and 0.63 ± 0.21 ug/ml after 2% mepivacaine with levonorfedrin. These differences were not statistically significant overall or at any time period.

- Safety results

No toxic reactions to the local anaesthetic were observed. However, because of the higher concentration of mepivacaine in the 3% formulation, it was potentially 1.5 times as toxic ($P < 0.002$) on a volume basis.

Summary

The authors conclude that 3% mepivacaine should not be used when relatively large volumes of local anaesthetic must be administered to small children and recommend that the maximum dose of mepivacaine not exceed 5mg/kg.

Assessors comments: Although there were no statistically significant differences in mean serum concentrations after a normalised dose of 1mg/kg body weight between 3% mepivacaine and 2% mepivacaine with vasoconstrictor, for safety reasons 3% mepivacaine should not be used when relative large volumes of mepivacaine must be administered to small children (2-5 years) and the maximum dose of mepivacaine should not exceed 5mg/kg. However, in 4.2. of the SmPC 4mg/kg body weight should not be exceeded. This discrepancy should be clarified. Moreover, no differentiation in children weighing 20-30kg and 30-45kg, respectively according to 4.2. of the SmPC has been described. An age range of 2-5 years has been given only. Therefore the posology for children in 4.2. of the SmPC can not be verified from the data of this study.

3) *College, C., Feigal, R., Wandera, A. et al.*

Description

Bilateral versus unilateral mandibular block anaesthesia in a paediatric population.
Paediatric Dent. 2000, 22 (6) 453-457

Methods

- **Objective(s)**
To evaluate unilateral versus bilateral mandibular nerve block anaesthesia with regard to post-operative soft tissue trauma and other complications in a pediatric population.
- **Study design**
Open, comparative study. Two separate treatment groups were examined: the control group received unilateral mandibular block anaesthesia, while the experimental group received bilateral mandibular block anaesthesia. Subjects were evenly divided in both groups and also when grouped by age. 2 types of local anaesthetics used: 2% lidocaine HCl with 1:100.000 epinephrine (in 97% of patients, n=310) and 2% mepivacaine HCl with 1:20.000 levonorfedrin (3% of patients, n=10). The maximum recommended dose was used.
- **Outcomes/endpoints**
Soft tissue trauma (redness and/or swelling on the lip, cheek or tongue). Speech or drooling difficulties, time of first meal after treatment and parent's subjective opinion as to whether or not their child accepted the numbness sensation.
- **Statistical methods**
Chi square analyses were utilised to compare incidence of trauma in each of these subgroups and to compare other trends within the population of patients. Subjects were divided into one of 4 age groups and Chi Square analysis was used to evaluate any differences among age groups.

Results

- **Recruitment/ Number analysed**
320 patients, age 2 to 18 years. There were no age, gender, behaviour or general health exclusions.
- **Baseline data**
N/A
- **Efficacy results**
Trauma frequency was 18% (<4 years), 16% (4-7 yrs.), 13% (8-11yrs.) and 7% (>12yrs.). Comparing unilateral versus bilateral subjects as to trauma revealed that in the <4 age group trauma was higher for the unilateral subjects (35% vs. 5%, P<.02). Non-significant trends showed increased trauma in unilateral groups at ages 8-11 and >12 years.
- **Safety results**
Not reported.

Summary

Frequency of post anaesthesia soft tissue trauma was higher in young patients and decreased with age. There was no significant difference in the incidence of trauma between bilateral and unilateral groups. In fact, there was a tendency for patients anaesthetised in both mandibular quadrants to experience less soft tissue trauma than the unilateral control group. In relation to post-operative soft tissue trauma and patient/parent report of subjective factors, there is no contraindication to the use of bilateral inferior alveolar nerve block anaesthesia in a paediatric population.

Assessors comments: Frequency of post anaesthesia soft tissue trauma was higher in young patients (<4 years) and decreased with age (4->12 years).

There was no significant difference in the incidence of trauma between bilateral and unilateral groups except in the age group (<4 years) where trauma was higher for the unilateral subjects (35% vs. 5%, $P<.02$).

There is no contraindication to the use of bilateral inferior alveolar nerve block anaesthesia in a paediatric population.

In this study 2% lidocaine with vasoconstrictor has been used in 97% of patients (2-18 years) and 2% mepivacaine with vasoconstrictor in only 3% of patients.

Safety data are missing.

Exact dosage is missing

This publication does not provide any information regarding the categorisation in children weighing 20-30kg and 30-45kg, respectively according to 4.2. of the SmPC.

Therefore the posology for children in 4.2. of the SmPC can not be verified from the data of this study.

4) Sharaf,A.A.

Description

Evaluation of mandibular infiltration versus block anaesthesia in paediatric dentistry.

ASDC. J. Dent. Child. 1997. 64 (4) 276-281.

Methods

- Objective(s)
To compare the clinical effectiveness of mandibular infiltration anaesthesia and mandibular block anaesthesia for the operative treatment, pulp therapy and extraction of primary molars and to measure patients acceptability of both techniques.
- Study design
Open comparative study, randomised application of mepivacaine HCl 2% (volume missing) to each side of block or infiltration anaesthesia. Topical anaesthetic was applied before injection in both techniques.
- Outcomes/endpoints
Frankl behaviour classification to measure reaction to pain:

Table 3 □ Frank Behavioral Scale (Frank et al 1962) used to measure cooperative behavior.

Rating 1:	Definitely negative Refusal of treatment, crying forcefully, fearful, or any other overt evidence of extreme negativism
Rating 2:	Negative Reluctant to accept treatment, uncooperative, some evidence of negative attitude but not pronounced (i.e. sullen, withdrawn)
Rating 3:	Positive Acceptance of treatment, at times cautious; willingness to comply with the dentist, at times with reservation, but patient follows the dentist's directions cooperatively
Rating 4:	Definitely positive Good rapport with the dentist interested in the dental procedures, laughing and enjoying

Sounds, eyes and motor scale (SEM).

Table 2 □ The SEM scale used to measure comfort or pain.

Observations	1. Comfort	2. Mild discomfort	3. Moderately painful	4. Painful
Sounds	No sounds indicating pain	Nonspecific sounds; possible pain indication	Specific verbal complaints, e.g., "OW", raises voice	Verbal complaint indicates intense pain, e.g., scream, sobbing
Eyes	No eye signs of discomfort	Eyes wide, show of concern, no tears	Watery eyes, eyes flushing	Crying, tears running down face
Motor	Hands relaxed; no apparent body tenseness	Hands show some distress or tension; grasps chair due to discomfort, muscular tension	Random movement of arms or body without aggressive intention of physical contact, grunts, twitch	Movement of hands to make aggressive physical contact, e.g., punching, pulling head away

- Statistical methods
Paired t-test.

Results

- Recruitment/ Number analysed
Recruitment: Group 1: 3-5yrs. n=25. Group 2: 5-7yrs. n=25. Group 3: 7-9yrs. n=30.
Number analysed: Group 1: 3-5yrs. n=5-20, Group 2: 5-7yrs. n=5-20, Group 3: 7-9yrs. n=5-30.
- Baseline data

Table 1 □ Distribution of patients and type of treatment.

Group	Extraction		Restorations		Pulpotomy	
	1st try molar	2nd try molar	1st try molar	2nd try molar	1st try molar	2nd try molar
I. 3-5Y n=25	5	—	5	5	5	5
II. 5-7Y n=25	5	—	5	5	5	5
III. 7-9Y n=30	5	5	5	5	5	5

- Efficacy results

Table 4 □ Pain reaction during injection of the needle using SEM scale.

	Infiltration	Block	Significance
3-5Y n=25	1.32 ± 0.39	2.36 ± 0.65	P=0.000(S)
5-7Y n=25	1.24 ± 0.354	2.013 ± 0.773	P=0.000(S)
7-9Y n=30	1.11 ± 0.22	1.96 ± 0.572	P=0.000(S)

S = Significant

Table 6 □ Behavior and pain reaction during rubber dam placement.

Age group	Tooth	Behavior		SEM	
		Infiltration	Block	Infiltration	Block
3-5Y n=10	D	3.2 ± 0.42	2.4 ± 0.52	1.00	1.97 ± 0.82
	E	3.3 ± 0.46	2.5 ± 0.71	1.2 ± 0.32	1.87 ± 0.53
5-7Y n=10	D	3.6 ± 0.51	3.2 ± 0.42	1.1 ± 0.16	1.53 ± 0.42
	E	3.5 ± 0.53	3.2 ± 0.63	1.16 ± 0.47	1.53 ± 0.5
7-9Y n=10	D	4	3.6 ± 0.52	1.00	1.3 ± 0.37
	E	3.9 ± 0.32	3.4 ± 0.52	1.03 ± 0.11	1.47 ± 0.36

S = Significant

NS = Nonsignificant

D = 1st primary molar

E = 2nd primary molar

Table 7 Behavior and pain reaction during placement of extraction forceps.

Age-group	Tooth	Behavior		SEM	
		Infiltration	Block	Infiltration	Block
3-5Y n=5	D	3.2±0.45	2.4±0.55	1.4±0.28	2.2±0.77
		P = 0.016 S		P = 0.009 NS	
5-7Y n=5	D	3.4±0.55	3.2±0.45	1.33±0.31	1.47±0.3
		P = 0.374 NS		P = 0.178 NS	
7-9Y n=5	D	4	3.6±0.55	1.2±0.3	1.27±0.28
		P = 0.178 NS		P = 0.374 NS	
n=10	E	4	3.6±0.55	1.2±0.3	1.6±0.37
		P = 0.178 NS		P = 0.07 NS	

S = Significant
NS = Nonsignificant
D = 1st primary molar
E = 2nd primary molar

Table 8 Behavior and pain reaction during entering dentin.

Age-group	Tooth	Behavior		SEM	
		Infiltration	Block	Infiltration	Block
3-5Y n=10	D	3.9±0.32	3.2±0.42	1.00	1.33±0.42
		P = 0.001 S		P = 0.022 S	
n=20	E	3.7±0.48	3.5±0.53	1.2±0.32	1.43±0.52
		P = 0.443 NS		P = 0.257 NS	
5-7Y n=30	D	4	4	1	1
		P = 0.374 NS		P = 0.374 NS	
n=20	E	3.74±0.67	3.3±0.42	1.16±0.47	1.53±0.5
		P = 0.591 NS		P = 0.061 NS	
7-9Y n=10	D	4	4	1	1
		P = 0.374 NS		P = 0.374 NS	
n=20	E	3.7±0.48	3.6±0.42	1.17±0.36	1
		P = 0.343 NS		P = 0.177 NS	

S = Significant
NS = Nonsignificant
D = 1st primary molar
E = 2nd primary molar

Table 9 Behavior and pain reaction during tooth movement in extractions.

Age-group	Tooth	Behavior		SEM	
		Infiltration	Block	Infiltration	Block
3-5Y n=5	D	3.6±0.55	3.2±0.45	1.27±0.37	1.73±0.25
		P = 0.178 NS		P = 0.108 NS	
5-7Y n=5	D	3.8±0.45	3.4±0.55	1.13±0.18	1.47±0.3
		P = 0.374 NS		P = 0.034 NS	
7-9Y n=5	D	4	4	1.13±0.18	1.27±0.25
		P = 0.178 NS		P = 0.178 NS	
n=10	E	4	3.8±0.45	1.13±0.18	1.33±0.41
		P = 0.374 NS		P = 0.374 NS	

NS = Nonsignificant
D = 1st primary molar
E = 2nd primary molar

Table 10 Behavior and pain reaction upon entering the pulp in mandibular first primary molars.

Age-group	Behavior		SEM	
	Infiltration	Block	Infiltration	Block
3-5Y (n=5)	4	3.6±0.55	1	1.067±0.15
	P = 0.178 NS		P = 0.374 NS	
5-7Y (n=5)	4	4	1	1
	P = 0.374 NS		P = 0.374 NS	
7-9Y (n=5)	4	4	1	1
	P = 0.374 NS		P = 0.374 NS	

NS = Nonsignificant

Table 11 Incidence of failure of infiltration anaesthesia upon entering the pulp in mandibular second primary molars.

3-5Y (n=5)	5-7Y (n=5)	7-9Y (n=5)
(2/5) = 40%	(3/5) = 60%	(3/5) = 60%

- Safety results Not reported.

Summary

Buccal infiltration anaesthesia is effective in providing good anaesthesia for restorative work and for extractions, when supplemented by interpapillary injections in mandibular primary molars regardless of age (3-9 years).

Buccal infiltration anaesthesia is effective in providing good anaesthesia for pulp treatment in mandibular first primary molars regardless of age.

Buccal infiltration anaesthesia is not reliable in obtaining profound anaesthesia for pulp treatment of mandibular second primary molars.

Block anaesthesia can change negatively the behavior of children ages three to five years and is significantly more painful than buccal infiltration anaesthesia.

Assessors comments: The paired t-test is not the appropriate statistical method for this kind of comparison dealing with categorical endpoints.

Safety data are missing.

This publication does not provide any information regarding the categorisation in children weighing 20-30kg and 30-45kg, respectively according to 4.2. of the SmPC.

Moreover, not even the volume of 2% mepivacaine applied is declared. It is not clear if a vasoconstrictor has been added to the 2% mepivacaine as in the other publications or not. Only the age range 3-9 years has been given.

Therefore the posology for children in 4.2. of the SmPC can not be verified from the data of this study.

5) Wright, G.Z., Weinberger, S.J., Marti, R. et al.,

Description

The effectiveness of infiltration anaesthesia in the mandibular primary molar region.

Paediatric Dent. 1991, 13 (5) 278-283.

Methods

- Objective(s)
To determine the effectiveness of infiltration anaesthesia in the mandibular primary molars, and how patient age, tooth location and anaesthetic type relate to the quality of anaesthesia.
- Study design
Double-blind study in 66 children, 35 males and 31 females, 42-72 months old. Infiltration anaesthesia (1.0 ml) with mepivacaine hydrochloride 2% (Carbocaine®), prilocaine hydrochloride 4% (Citanest Forte®) and articaine hydrochloride 4% (Ultracaine® DS), all containing epinephrine 1:200.000.
- Outcomes/endpoints

a) The SEM scale to measure subject comfort or pain:

Table 1. The SEM scale used to measure comfort or pain

Observations	Comfort or Pain Level			
	1. Comfort	2. Mild Discomfort	3. Moderately Painful	4. Painful
Sounds	No sounds indicating pain	Nonspecific sounds; possible pain indication	Specific verbal complaints, e.g., "OW", raises voice	Verbal complaint indicates intense pain, e.g., scream, sobbing
Eyes	No eye signs of discomfort	Eyes wide, show of concern, no tears	Watery eyes, eyes flinching	Crying, tears running down face
Motor	Hands relaxed; no apparent body tenseness	Hands show some distress or tension; grasps chair due to discomfort, muscular tension	Random movement of arms or body without aggressive intention of physical contact, grimace, twitch	Movement of hands to make aggressive physical contact, e.g., punching, pulling head away

b) Frankl Behavior Scale to measure children's behavior.

Table 2. Frankl Behavioral Scale (Frankl et al. 1962) used to measure cooperative behavior

Rating 1:	Definitely negative Refusal of treatment, crying forcefully, fearful, or any other overt evidence of extreme negativism
Rating 2:	Negative Reluctant to accept treatment, uncooperative, some evidence of negative attitude but not pronounced (i.e., sullen, withdrawn)
Rating 3:	Positive Acceptance of treatment; at times cautious; willingness to comply with the dentist, at times with reservation, but patient follows the dentist's directions cooperatively
Rating 4:	Definitely positive Good rapport with the dentists interested in the dental procedures, laughing and enjoying

All experimental procedures were videotaped.

- Statistical methods
Data derived from both of these scales were dichotomised when statistical analysis were performed. Dichotomised data were analysed by a Chi-square analysis. A significance level of 0.05 was used.

Results

- Recruitment/ Number analysed
Initial study population consisted of 75 children. However, the results derived from 66 children, 35 males and 31 females, 42-72 months old. 6 children were eliminated because their behaviour did not allow reasonable pain evaluation and 3 children were omitted because of technical problems during videotaping.
- Baseline data
N/A
- Efficacy results

Table 3. Comfort or pain assessment using infiltration anesthesia for mandibular molars

Subjects	Injection	Evaluation Intervals		
		Probe	Rubber Dam	Preparation
All subjects	39/66 (59%)	55/66 (83%)	53/66 (80%)	43/66 (65%)
No injection pain	—	35/39 (90%)	35/39 (90%)	28/39 (72%)
Injection pain	—	20/27 (74%)	18/27 (67%)	15/27 (56%)

Table 5. Relationship between comfort or pain and cooperative behavior

	Injection	Evaluation Intervals		
		Probe	Rubber Dam	Preparation
Comfort/cooperative	39/56 (70%)	53/63 (84%)	52/59 (88%)	42/57 (74%)
Comfort/uncooperative	0/10 (0%)	2/3 (67%)	1/7 (14%)	1/9 (11%)

Table 6. The relationship of three variables — age of patient, tooth and anesthetic type to the quality of mandibular infiltration anesthesia

		Evaluation Intervals		
		Probe	Rubber Dam	Drill
Age	42 mo. to 59 mo.	30/35 (86%)	28/35 (80%)	18/35 (51%)
	60 mo. to 78 mo.	25/31 (81%)	25/31 (81%)	25/31 (81%)
Tooth	1° molar	28/35 (80%)	25/35 (71%)	25/35 (71%)
	2° molar	27/31 (87%)	28/31 (90%)	18/31 (58%)
Anesthetic Type	Citanest	15/19 (70%)	16/19 (84%)	11/19 (58%)
	Ultracaine DS	22/25 (88%)	17/25 (68%)	17/25 (68%)
	Carbocaine 2%	18/22 (82%)	20/22 (91%)	15/22 (68%)

- Safety results
Not reported.

Summary

- 65% of the subjects experienced little or no pain.
- Children who demonstrated little or no pain during injection were likely to be comfortable during successive procedures
- There was a high relationship between children behaving cooperatively and comfort during procedures
- The quality of anaesthesia was not significantly related to tooth location, age, or type of anaesthetic agent.

Assessors comments: 82%, 91% and 68% of the subjects (22 children, 42-72 months = 3,5-6 years old) experienced little or no pain after infiltration anaesthesia with 1.0ml mepivacaine 2% containing a vasoconstrictor. Children who demonstrated little or no pain during injection were likely to be comfortable during successive procedures.(This applies to all 3 local anaesthetics:mepivacaine 2%, prilocaine 4% and articaine 4%, all containing a vasoconstrictor).

There was a high relationship between children behaving cooperatively and comfort during procedures.

The quality of anaesthesia was not significantly related to tooth location, age or type of anaesthetic agent.

However:

Safety data are missing.

This publication does not provide any information regarding the categorisation in children weighing 20-30kg and 30-45kg, respectively according to 4.2.of the SmPC. An age range of 3.5-6 years has been given only.

Therefore the posology for children in 4.2. of the SmPC can not be verified from the data of this study.

3. Discussion on clinical aspects

In the SmPC for Mepivastesin 30mg/ml (3% without vasoconstrictor) provided by 3M ESPE the posology for children is as follows:

“In children weighing about 20-30kg, doses of 0.25-1ml are sufficient; and in children weighing 30-45kg, 0.5-2ml.

Maximum recommended dosage:

Children:

The quantity to be injected should be determined by the age and weight of the child and the magnitude of the operation. Do not exceed the equivalent of 4mg mepivacaine/kg (0.133ml Mepivastesin/kg) of body weight.”

From the submitted eight studies in only 4 studies mepivacaine 3% has been used. The remaining studies used 2% mepivacaine with a vasoconstrictor.

Neither of the submitted eight studies presented data which would corroborate the posology for children proposed in the SmPC.

From 02.11.2009 there was a **clock-stop period** until 05.02.2010.

The **MA Holder 3M ESPE** submit a scientific argumentation and documentation for filing an objection against the decision of the rapporteur with the following new paediatric dose recommendations and conclusion:

New proposed recommended therapeutic dose:

“The quantity to be injected should be determined by the age and weight of the child and the magnitude of the operation.

The average dosage is 0.025 ml of Mepivastesin solution per kg body weight.

Maximum recommended dosage:

Do not exceed the equivalent of 3 mg mepivacaine/kg (0.1 ml Mepivastesin/kg) of body weight.

Conclusion 3M ESPE:

Mepivacaine 3 % has been used over more than 30 years in dentistry particularly in paediatric dentistry. The safety and efficacy level of this drug has been proven over three decades. The monitoring by pharmacovigilance of the drug substance results in no signal to paediatric risk.

The result of the presented assessment report of the rapporteur to contraindicate practically the use of mepivacaine 3% in children and adolescents in dentistry (0-18 years of age) cannot be justified due to the well established use of the substance. Although the presented studies gave no detailed information about the therapeutical recommended dosage of mepivacaine in children, the safety and efficacy level have been proven in presented studies.

Due to the clinical requirements and based on the clinical experience on efficacy and safety, the MAH of Mepivacaine 3% for infiltration and conduction anaesthesia in the paediatric population suggests the following limits for use:

1. Mepivacaine 3% should not be used in children below 4 years of age.
2. The maximum recommended dose of mepivacaine in children is based on the presented literature and calculated to 3 mg per kg body weight of the children.

Considering the major objection of the CMS UK to the proposed modification of section 4.2 of the SPC and the aim of the regulation to facilitate the accessibility of medicinal products for use in the paediatric population (see article 4, 5 and 45 of the regulation no 1901/2006) the deletion of the paediatric dosage for mepivacaine 3 % is not justified.

We apply therefore to revise the assessment report according to the proposed SPC posology recommendation.

Assessor’s comment: On assessing the responses following questions arises:

- 1) Please justify the proposed usual dose of 0.75mg/kg BW (0.025 ml/kg BW) and
- 2) Please justify the maximal allowed dose of 3mg/kg BW, as these doses are lower as those calculated according to AHFS adapted formula.

SmPC: to be added:

4.2. Children from 4 years of age (20kg BW) and older

4.3. - children below 4 years of age (20kg BW)

Response 3M ESPE:

Newly suggested dose recommendations for children at 4 years of age and older that are reduced in comparison to the dose recommendations for mepivacaine 3% approved by the FDA to a therapeutic dose of 0.75 mg/kg BW and a maximum allowed single dose of 3 mg/kg per session were justified by arguments in favour of increased safety. Relative overdosage in patients weighing 20-30 kg is avoided by strictly calculating the dose per kg BW. This approach provides higher safety and should be applicable regarding the special local bone conditions.

Instead of higher doses of local anaesthetics, appropriate complex measures are recommended in order to guarantee painless and relaxed paediatric dental sessions.

Assessor's comment: I agree to your scientific argumentation in support of the newly proposed usual doses for children, dated 7.1.2010. Therefore I propose the following changes to 4.2. and 4.3. of the present SmPC:

4.2. Children from 4 years of age (ca.20kg body weight) and older (see 4.3.)

Recommended therapeutic dose:

The quantity to be injected should be determined by the age and weight of the child and the magnitude of the operation. The average dosage is 0.75mg/kg=0.025ml of mepivacaine solution per kg body weight.

Maximum recommended dosage:

Do not exceed the equivalent of 3mg mepivacaine/kg (0.1ml mepivacaine/kg) of body weight.

4.3. *to be added*

children below 4 years of age (ca.20kg body weight).

The MA Holder 3M ESPE accepted the changes in the SmPC.

The **MA Holder Septodont** sent their response that they do not agree with the assessment report's conclusion and wish to maintain the claimed posology for children in the SmPC. Their conclusion was that the efficacy and safety of injected mepivacaine from 1% to 3% with or without vasoconstrictor in children is well established in multiple situations. The regional anaesthesia for pain control in different paediatric situations (post-operative pain after general anaesthesia, urologic procedures, herniorrhaphy, dental extraction) at doses up to 11mg/kg, a wide variety of paediatric indications are covered underlining the safety of the use in infiltration anaesthesia and nerve block in dentistry.

Assessor's comment: The provided references add only some new data supporting the dosage recommendation in the present SmPC in children:

"In children weighing about 20-30kg, doses of 0.25-1ml are sufficient; and in children weighing 30-45kg, 0.5-2ml. The quantity to be injected should be determined by the age and weight of the child and the magnitude of the operation. Do not exceed the equivalent of 4mg mepivacaine/kg (0.133ml mepivacaine/kg) of body weight."

According to "AHFS Mepivacaine hydrochloride. American Hospital Formulary Service Drug Information 2010" the maximum pediatric dose can be calculated as follows:

Maximum dose (in mg) = (child's weight (in pounds)/150) x 400mg. For a child with 20kg = 44 pounds this results in 117mg = ca.120mg. This would be 6mg/kg. As this dose would be higher than the maximum dose for adults = 4mg/kg and for safety reasons we recommend to lower the maximum dose to 3mg/kg. For the therapeutic dose we recommend 0.75mg/kg as this is approximately the average dose given in the present SmPC for children with 20-30kg = 0.25-1ml. These dosage recommendations would apply to children from 4 years of age (ca. 20kg) and older. In children below of 4 years (ca.20kg) mepivacaine should be contraindicated for safety reasons as concentrations less than 3% should be used

(Berquist H.C.1975, AHFS 2010) and there is no dose recommendation in the present SmPC for children below 20kg = 4years.

Therefore 4.2. in the SmPC would read:

Children from 4 years of age (ca.20kg body weight) and older (see 4.3.)

Recommended therapeutic dose:

The quantity to be injected should be determined by the age and weight of the child and the magnitude of the operation. The average dosage is 0.75mg/kg=0.025ml of mepivacaine solution per kg body weight.

Maximum recommended dosage:

Do not exceed the equivalent of 3mg mepivacaine/kg (0.1ml mepivacaine/kg) of body weight.

4.3. to be added

children below 4 years of age (ca.20kg body weight).

Response Septodont:

Septodont bases its recommendations for maximal dose on the Malamed's "Handbook for Local Anaesthesia" 5th Edition. In his book, Malamed gives for Mepivacaine the following maximum recommended dose :

4.4mg/kg or 300mg as absolute dose.

(I enclose a scanned copy of the selected page on Mepivacaine for your convenience - MRD-m = Maximum Recommended Dose of the manufacturer / MRD-a=Maximum Recommended Dose of the author)

This applies also to paediatric patients.

This would represent about 176mg of mepivacaine for a 40kg child, which is the half of the absolute recommended dose.

For a 20kg child, it is 88mg which is more than 3 time less of the absolute recommended dose.

So Septodont would like to keep 4mg mepivacaine/kg of body weight as maximum recommended dose as initially proposed.

Regarding the contraindication of using mepivacaine 3% in children below 4, we totally agree with this proposal.

Therefore, we would read

4.2. regarding paediatric population:

Children from 4 years of age (ca.20kg body weight) and older (see 4.3.)

Recommended therapeutic dose:

The quantity to be injected should be determined by the age and weight of the child and the magnitude of the operation. The average dosage is 0.75mg/kg=0.025ml of mepivacaine solution per kg body weight.

Maximum recommended dosage:

Do not exceed the equivalent of 4mg mepivacaine/kg (0.1ml mepivacaine/kg) of body weight.

4.3. to be added

children below 4 years of age (ca.20kg body weight).

Assessor's comment: The maximum dose for adults is 4mg/kg. However, due to special conditions in paediatric dentistry as lower bone density enabling better penetration of the local anaesthetic I would strongly recommend to lower the maximum dose for children to the proposed 3mg/kg. I wonder that in Malamed's Handbook for local anaesthesia this fact is not considered. Moreover, in daily practice it is more practicable to administer 0,1ml/kg than 0,133ml/kg BW.

Response Septodont:

Septodont accepts 3 mg/kg (0.1 ml/kg) as the maximum dose for children.
Therefore the MA Holder Septodont accepted the changes in the SmPC.

V. MEMBER STATES OVERALL CONCLUSION AND RECOMMENDATION

➤ **Overall conclusion**

Eight studies has been submitted by the three MAH SEPTODONT(FR), 3M ESPE (DE) and N.V.Denta S.A.(BE) to support the posology of mepivacaine 30mg/ml for children given in the SmPC for the therapeutic indications: “Infiltration anaesthesia and nerve-block in dentistry. Mepivastesin is indicated for simple extractions as well as cavity and stump preparations. Mepivastesin is especially suitable for patients to whom vasoconstricting additives are contraindicated.”

From these studies in only 4 studies mepivacaine 3% has been used. Neither of these studies provided adequate data to support the claimed posology for children in the SmPC.

Neither the studies using 2% mepivacaine with vasoconstrictor corroborated the claimed posology.

Both MA Holder 3M ESPE and Septodont opposed the Assessor’s initial recommendation by scientific argumentation and documentation which has been accepted by the assessor and resulted in an alternative wording in 4.2. and 4.3. of the SmPC.

➤ **Recommendation**

The claimed posology for mepivacaine 30mg/ml in children as a local anaesthetic in dentistry should be changed as follows:

Proposed changes in the SmPC:

4.2. *The present text should be deleted:*

In children weighing about 20-30kg, doses of 0.25-1ml are sufficient; and in children weighing 30-45kg, 0.5-2ml.

Children:

The quantity to be injected should be determined by the age and weight of the child and the magnitude of the operation. Do not exceed the equivalent of 4mg mepivacaine/kg (0.133ml Mepivastesin/kg) of body weight.

and replaced by

4.2. Children:

Children from 4 years of age (ca.20kg body weight) and older (see 4.3.)

Recommended therapeutic dose:

The quantity to be injected should be determined by the age and weight of the child and the magnitude of the operation. The average dosage is 0.75mg/kg = 0.025ml of mepivacaine solution per kg body weight.

Maximum recommended dosage:

Do not exceed the equivalent of 3mg mepivacaine/kg (0.1ml mepivacaine/kg) of body weight.

4.3. *to be added*

children below 4 years of age (ca.20kg body weight).

A Type IB variation to be requested from the MAH by day 180 of the procedure.

VI. LIST OF MEDICINAL PRODUCTS AND MARKETING AUTHORISATION HOLDERS INVOLVED

Mepivastesin 30mg/ml solution for injection, 3M ESPE AG., ESPE Platz, D-82229 Seefeld..

Scandonest 30mg/ml solution for injection, SEPTODONT, 58, rue du Pont de Creteil,
94107 Saint-Maur-des-Fosses Cedex.

Mepivastesin 30mg/ml solution for injection, N.V. Denta S.A., Heiveldekens 2, B-2550 Kontich.