

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
22-466

OTHER REVIEW(S)



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: February 22, 2010

To: Bob Rappaport, MD, Director
Division of Anesthesia, Analgesia and Rheumatology
Products

Through: Kristina C. Arnwine, PharmD, Team Leader
Denise Toyer, PharmD, Deputy Director
Division of Medication Error Prevention and Analysis

From: Tselaine Jones Smith, PharmD, Safety Evaluator
Division of Medication Error Prevention and Analysis

Subject: Labeling Review

Drug Name: Articaïne Hydrochloride 4% with Epinephrine 1:100,000
Injection; and,
Articaïne Hydrochloride 4% with Epinephrine 1:200,000
Injection

Application Type/Number: NDA 022466

Applicant: Pierrell S.p.A.

OSE RCM #: 2010-131

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1 BACKGROUND

1.1 INTRODUCTION

This review is written in response to a January 14, 2010 request from the Division of Anesthesia, Analgesia and Rheumatology Products for evaluation of the labels and labeling for Articaine Hydrochloride 4% with Epinephrine 1:100,000 Injection and Articaine Hydrochloride 4% with Epinephrine 1:200,000 Injection to identify areas that could contribute to medication errors. The Applicant submitted proposed cartridge labels, carton and insert labeling for our review.

1.2 REGULATORY HISTORY

DMEPA previously reviewed the labels and labeling for this product (submitted June 22, 2009) in OSE Review # 2008-2060, dated August 14, 2009. At the conclusion of the first review cycle of the subject NDA, the application received a Complete Response action, dated September 23, 2009. DMEPA's proposed label and labeling recommendations were included in this letter. On December 28, 2009, the Applicant submitted a Complete Response Submission which included revised cartridge labels, carton and labeling.

2 METHODS AND MATERIALS

The Division of Medication Error Prevention and Analysis used Failure Mode and Effects Analysis (FMEA)¹ in our evaluation of the labels and labeling that were submitted on December 28, 2009 (see Appendices A and B).

3 RECOMMENDATIONS

We note the Applicant addressed the majority of DMEPA's cartridge label and carton labeling recommendations from our previous labeling review. However, we noted added areas where the presentation of information on the labels and labeling can be clarified and improved upon to minimize the potential for medication errors. We provide recommendations on the insert labeling in Section 3.1, *Comments to the Division*. Section 3.2, *Comments to the Applicant*, contains our recommendations for the cartridge labels and carton labeling. We request the recommendations in Section 3.2 be communicated to the Applicant, prior to approval.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have questions or need clarifications, please contact OSE Project Managers, Abolade Adeolu at 301-796-4264 or Cheryle Milburn at 307-796-2084.

3.1 COMMENTS TO THE DIVISION

3.1.1 Proprietary Name Review

The proposed proprietary name (b) (4) was found to be unacceptable in OSE Review # 2009-1237, dated October 9, 2009. On January 19, 2009, the Applicant submitted a request for the review of an alternate proprietary name. The proposed proprietary name, (b) (4) is undergoing DMEPA review and the outcome of the review will be communicated in a review at a future

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

date. A labeling supplement will have to be submitted by the Applicant reflecting the proposed proprietary name.

3.1.2 *Package Insert Labeling*

1. Include units of measure with each notation of dose throughout the insert labeling. For example, 0.5 mL – 2.5 mL, 68 mg, etc.
2. Ensure that the established names and product strengths are presented in the same format throughout the labels and labeling:
Articaine hydrochloride 4% and Epinephrine 1:100,000
Articaine hydrochloride 4% and Epinephrine 1:200,000
3. Remove the statement [REDACTED] (b) (4) from the dosage form statement. The correct presentation of the proprietary name, established names, and dosage form should read as ‘Tradename (Articaine Hydrochloride and Epinephrine) Injection’

3.2 COMMENTS TO THE APPLICANT

Carton Labeling

1. Ensure that the established names and product strengths are presented in the same format throughout the labels and labeling:
Articaine hydrochloride 4% and epinephrine 1:100,000
Articaine hydrochloride 4% and epinephrine 1:200,000
2. In your December 28, 2009 resubmission, you state that the ‘Rx Only’ statement was removed from the two main faces. However, DMEPA notes that the statement was not relocated to another portion of the labeling. Revise the labeling to include the [REDACTED] (b) (4) on the side panel.
3. In the ‘Each mL contains’ statement on the principal display panel of Articaine 4% and Epinephrine 1:100,00, the strength of epinephrine per milliliter is presented as [REDACTED] (b) (4) rather than 0.0018 mg for epinephrine 1:100,000. Revise accordingly.
4. We acknowledge your agreement to increase the prominence of the established name once the pending proposed proprietary name is found acceptable. However, in the event you choose to market this product without a proprietary name, ensure that the prominence of established name is increased as the established name will be used to identify the product.

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| Application Type/Number | Submission Type/Number | Submitter Name | Product Name |
|-------------------------|------------------------|----------------|--|
| NDA-22466 | ORIG-1 | PIERREL S.P.A. | ARTICAINE 4% /EPINEPHRINE 1:20000 INJ |

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/s/

TSELAIN E JONES SMITH
02/22/2010

KRISTINA C ARNWINE
02/22/2010

DENISE P TOYER
02/22/2010

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

****PRE-DECISIONAL AGENCY MEMO****

DATE: August 17, 2009

To: Ayanna Augustus – Regulatory Project Manager
Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP)

From: Mathilda Fienkeng – Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC) *mfiengkeng*

Subject: **DDMAC draft labeling comments**
NDA 22-466 ARTICAINE WITH EPINEPHRINE 1:100,000; ARTICAINE WITH
EPINEPHRINE 1:200,000 (articaine hydrochloride 4% (40 mg/ml) with epinephrine
1:100,000 or 1:200,000) INJECTION

DDMAC has reviewed the proposed product labeling (PI) for ARTICAINE WITH EPINEPHRINE 1:100,000; ARTICAINE WITH EPINEPHRINE 1:200,000 (articaine hydrochloride 4% (40 mg/ml) with epinephrine 1:100,000 or 1:200,000) INJECTION, submitted for consult on December 12, 2008.

The following comments are provided using the updated proposed PI sent via email on August 5, 2009 by Ayanna Augustus. If you have any questions about DDMAC's comments, please do not hesitate to contact me at (301) 796 3692 or mathilda.fienkeng@fda.hhs.gov.

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/s/

MATHILDA K FIENKENG
09/15/2009

SEALD LABELING REVIEW

| | |
|--------------------|--|
| APPLICATION NUMBER | NDA 22-466 |
| APPLICANT | PIERREL |
| DRUG NAME | ARTICAINE 4% /EPINEPHRINE 1:20000 INJ |
| SUBMISSION DATE | November 25, 2008 |
| SEALD REVIEW DATE | August 14, 2009 |
| SEALD REVIEWER(S) | Abiola Olagundoye, PharmD |
| | This review does not identify all guidance-related labeling issues and all best practices for labeling. We recommend the review division become familiar with those recommendations. This review does attempt to identify all aspects of the draft labeling that do not meet the requirements of 21 CFR 201.56 and 201.57. |

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/s/

ABIOLA OLANGUNDOYE

08/20/2009

SEALD comments sent to DAARP on 8/14/09.

LAURIE B BURKE

08/20/2009



Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date: August 14, 2009

To: Bob Rappaport, MD, Director
Division of Anesthesia, Analgesia and Rheumatology Products

Through: Denise Toyer, PharmD, Deputy Director
Division of Medication Error Prevention and Analysis

From: Laura Pincock, PharmD, Acting Team Leader
Division of Medication Error Prevention and Analysis

Subject: Label and Labeling Review

Drug Name(s): Articaine Hydrochloride 4% with Epinephrine 1:100,000 Injection
and
Articaine Hydrochloride 4% with Epinephrine 1:200,000 Injection
1.8 mL cartridges

Application Type/Number: NDA # 22-466

Sponsor: Pierrell S.p.A.

OSE RCM #: 2008-2060

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1 INTRODUCTION

This review is written in response to a request from the Division of Anesthesia, Analgesia and Rheumatology Products for assessment of labels and labeling for [redacted] (b) (4) [Articaine Hydrochloride with Epinephrine Injection] for their vulnerability to medication errors.

2 METHODS AND MATERIALS

DMEPA used Failure Mode and Effects Analysis (FMEA) in our evaluation of the cartridge labels, carton, and insert labeling submitted as part of the June 22, 2009, amendment submission (see Appendix A and B).

3 CONCLUSIONS AND RECOMMENDATIONS

Our evaluation noted areas where information on the cartridge labels and carton labeling can be improved to minimize the potential for medication errors. We provide recommendations on the insert labeling in Section 2.1 *Comments to the Division* for discussion during the review team's label and labeling meetings. Section 2.2 *Comments to the Applicant* contains our recommendations for the container label and carton labeling. We request the recommendations in Section 2.2 be communicated to the Applicant prior to approval.

For this product the Applicant submitted cartridge labels and carton labeling on June 22, 2009, (See Appendix A and B):

- Cartridge labels: Articaine Hydrochloride 4% with Epinephrine 1:100,000 Injection and Articaine Hydrochloride 4% with Epinephrine 1:200,000 Injection
- Carton labeling: Articaine Hydrochloride 4% with Epinephrine 1:100,000 Injection and Articaine Hydrochloride 4% with Epinephrine 1:200,000 Injection

3.1 COMMENTS TO THE DIVISION

The proposed proprietary name for this product, [redacted] (b) (4), is undergoing DMEPA review and the outcome of this name review will be communicated in a review at a future date.

We defer to the Office of New Drug Quality Assessment for the correct determination of the established name and strength on the cartridge labels and carton labeling.

We have no comments on the insert labeling at this time.

3.2 COMMENTS TO THE APPLICANT

3.2.1 CARTRIDGE LABELS

1. The cartridge labels lack differentiation between the two strengths, since both are blue text on a white background. Use an alternate color (e.g., not blue) for one of the strengths to reduce the potential for confusion between the two strengths.

2. The net quantity statement (1.8 mL) immediately follows the established name, causing it to appear to be part of the product strength rather than a statement of the net quantity per cartridge. Relocate the net quantity statement to either the bottom of the label or the top left corner of the label, wherever space permits.

3.2.2 CARTON LABELING

1. The carton labeling lacks differentiation between the two strengths because both are yellow in color with a large blue stripe. Use an alternate color (e.g., not blue) for one of the strengths to reduce the potential for confusion between the two strengths.
2. The blue print on a blue background on the principal display panel is difficult to read. Consider a lighter color for the background or consider a different colored print to improve the readability of the important information on the principal display panel.
3. Increase the size of the established name so that it is at least one-half the size of the proprietary name in accordance with 21 CFR 201.10(g)(2), which states: the established name shall be printed in letters that are at least half as large as the letters comprising the proprietary name or designation with which it is joined, and the established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features.
4. Revise the net quantity statement to read “100 Cartridges each containing 1.8 mL” to more accurately describe the contents of the carton.

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/s/

LAURA L PINCOCK
08/14/2009

DENISE P TOYER
08/24/2009



Pediatric and Maternal Health Staff
Office of New Drugs
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Silver Spring, MD 20993
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Pediatric and Maternal Health Team Review

Date: July 17, 2009 **Date Consulted:** June 5, 2009

From: Jeanine Best, MSN, RN, PNP
Regulatory and Labeling Reviewer
Pediatric and Maternal Health Staff

Through: Karen Feibus, MD
Team Leader, Maternal Health Team (MHT)
Pediatric and Maternal Health Staff

Hari Cheryl Sachs, MD
Team Leader, Pediatric Team
Pediatric and Maternal Health Staff

Lisa Mathis, MD, OND Associate Director
Office of New Drugs - Immediate Office
Pediatric and Maternal Health Staff (PMHS)

To: Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP)

Drug: articaine hydrochloride and epinephrine bitartrate injection, solution,
NDA 22-466

Subject: Pregnancy, Nursing Mothers, and Pediatric Use labeling

Materials Reviewed:

- Pregnancy, Nursing Mothers, and Pediatric Use subsections of articaine hydrochloride and epinephrine bitartrate injection, solution labeling
- M.A. Goheer, Ph.D., Review and Evaluation of Pharmacology and Toxicology Data, NDA 20-971, August 28, 1998
- J. Filie, M.D., Clinical NDA Review, NDA 22-010, March 20, 2006
- S. Nallani, Ph.D. Clinical Pharmacology and Biopharmaceutics Review, NDA 22-010, February 27, 2006

Consult Question: Please review the Pregnancy, Nursing Mothers and Pediatric Use subsections of labeling.

INTRODUCTION

Pierrewl S.p.A. submitted a 505(b)(2) New Drug Application (NDA 22-466) on November 24, 2008, for articaine hydrochloride 4% with epinephrine 1:100,000 and 1:200,000, a local anesthetic agent, for the indication of local, infiltrative, or conductive anesthesia in both simple and complex dental procedures. This application, NDA 22-466, references the clinical studies from the referenced listed drug (RLD) applications, Septocaine® (NDAs 20-971 and 22-010), and the Sponsor requested a bioequivalence waiver, as the only differences from the RLD is an increased sodium chloride concentration, a higher pH, and a higher filling volume in this submitted NDA.

The Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP) requested that the Maternal Health Team (MHT) and the Pediatric Team of the Pediatric and Maternal Health Staff (PMHS) review the Pregnancy, Nursing Mothers, and Pediatric Use subsections of articaine hydrochloride and epinephrine bitartrate injection, solution labeling.

This review provides PMHS revisions to the sponsor's proposed Pregnancy, Nursing Mothers, and Pediatric subsections of articaine hydrochloride and epinephrine bitartrate injection, solution labeling.

BACKGROUND

Regulatory History

Articaine hydrochloride 4% with epinephrine 1:100,000 and articaine hydrochloride 4% with epinephrine 1:200,000 were submitted on March 30 1998, as NDA 20-971. Septocaine (articaine hydrochloride 4% with epinephrine 1:100,000) Injection was approved on April 3, 2000. Articaine hydrochloride 4% with epinephrine 1:200,000 was not approved at this time as all submitted clinical data was based on the articaine hydrochloride 4% with epinephrine 1:100,000 formulation. An Efficacy Supplement containing clinical data for articaine hydrochloride 4% with epinephrine 1:200,000, NDA 22-010, was submitted on September 30, 2005, and approved March 30, 2006, with the sponsor demonstrating that a meaningful clinical difference could be seen between the two formulations. Articaine hydrochloride 4% with epinephrine 1:100,000 is preferred during operative or surgical procedures when improved visualization of the surgical field is desirable.¹

A limited number of pediatric patients, ages 4 to 16 years of age, were included in the U.S. development plan using articaine hydrochloride 4% with epinephrine 1:100,000. Efficacy was demonstrated with this formulation and only minor adverse events were reported. Additional pediatric safety data from Europe showed few adverse events. No pediatric studies were conducted using articaine hydrochloride 4% with epinephrine 1:200,000; however, the pharmacokinetics of articaine were found to be similar in both adults and children,² and this formulation was approved for use in children ages 4 to 16 years of age based on the data from studies with articaine hydrochloride 4% with epinephrine 1:100,000. The Pediatric Research Equity Act (PREA) was not triggered because the original NDA containing both articaine formulations was submitted prior to April 1, 1999; however, the clinical reviewer³ suggested that the Sponsor be encouraged to submit a Proposed Pediatric Study Request (PPSR) for studies in children ages 2 to less than 4 years of age. No PPSR has been submitted to date.

Articaine hydrochloride 4% with epinephrine 1:100,000 and articaine hydrochloride 4% with epinephrine 1:200,000 were not studied in pregnant or lactating women; however, limited human lactation data is currently available.

¹ See Draft articaine hydrochloride and epinephrine bitartrate injection, solution labeling, November 24, 2009

² See S. Nallani, Ph.D. Clinical Pharmacology and Biopharmaceutics Review, NDA 22-010, February 27, 2006

³ See J. Filie, M.D., Clinical NDA Review, NDA 22-010, March 20, 2006

Pregnancy and Nursing Mothers Labeling

The Maternal Health Team (MHT) has been working to develop a more consistent and clinically useful approach to the Pregnancy and Nursing Mothers subsections of labeling. This approach complies with current regulations but incorporates “the spirit” of the Proposed Pregnancy and Lactation Labeling Rule (published on May 29, 2008). The MHT reviewer ensures that the appropriate regulatory language is present and that available information is organized and presented in a clear and useful manner for healthcare practitioners. Animal data in the pregnancy subsection is presented in an organized, logical format that makes it as clinically relevant as possible for prescribers. This includes expressing animal data in terms of species exposed, timing and route of drug administration, dose expressed in terms of human exposure or dose equivalents (with the basis for calculation), and outcomes for dams and offspring. For nursing mothers, when animal data are available, only the presence or absence of drug in milk is considered relevant and presented in the label, not the amount.

Pediatric Use Labeling

The Pediatric Use subsection should clearly describe what is known and what is unknown about use of a drug in children, including limitations of use. This subsection should also highlight any differences in efficacy or safety in children versus the adult population.

(b) (4)

DISCUSSION

In addition to reviewing the sponsor's submitted labeling, PMHS conducted its own PubMed search for literature on articaine and pregnancy, dental procedures during pregnancy, articaine and breastfeeding, and articaine and children. This reviewer also searched The Drug and Lactation Database (LactMed)⁴ for data on articaine use during lactation.

Note: PMHS did not have access to the sponsor's referenced clinical and nonclinical data used to inform this labeling.

⁴ The Drug and Lactation Database (<http://toxnet.nlm.nih.gov>)

Pregnancy

No clinical studies were conducted with articaine hydrochloride and epinephrine bitartrate in pregnant women, and no published information is available on the drug's use during pregnancy (b) (4)

There is published information regarding the importance of maintaining oral health throughout pregnancy and the use of local anesthetics for dental procedures during pregnancy. Periodontal disease during pregnancy can lead to adverse pregnancy outcomes including miscarriage, preeclampsia, preterm birth, stillbirth, and low infant birthweight.^{5,6} A study examining the safety of dental treatment during pregnancy showed a significant reduction in preterm births and low birth weight infants without apparent adverse fetal outcomes from the use of local anesthetics with dental procedures.⁷ Other research is not clear whether the treatment of periodontal disease during pregnancy improves pregnancy outcome or if periodontal disease needs to be treated before a pregnancy occurs in order to improve a pregnancy outcome.⁶ Available research does not demonstrate a signal for adverse fetal outcomes from local anesthetics used for dental procedures during a pregnancy, as long as care is maintained to avoid an intravascular injection.^{5,7}

Lactation

No clinical lactation studies were conducted with articaine hydrochloride and epinephrine bitartrate, and no published information is available regarding the excretion of articaine hydrochloride and epinephrine bitartrate into human milk. The Drug and Lactation Database (LactMed)⁸ and published data⁹ on the use of other local anesthetics used for dental procedures show a rapid metabolism of these drugs, poor systemic bioavailability, low excretion into human milk, and poor absorption in nursing infants. The American Academy of Pediatrics (AAP)¹⁰ classifies local anesthetics used for dental procedures as "usually compatible with breastfeeding." Articaine hydrochloride and epinephrine bitartrate injection is used solely during dental procedures and has a relatively short elimination half-life of 45 minutes. Because of the drug's short half-life, a nursing mother may choose to pump and discard breast milk for five half-lives (approximately 4 hours) after an articaine hydrochloride and epinephrine bitartrate injection in order to minimize potential infant ingestion.

Pediatrics

A limited number of pediatric patients, ages 4 to 16 years of age, were included in the U.S. development plan using articaine hydrochloride 4% with epinephrine 1:100,000, and only minor adverse events were reported. Adewumi, et al¹¹ conducted a prospective study in 264 children ages 2 to 14 years who received articaine for restorative dental procedures. Adverse event data regarding prolonged paresthesia, soft tissue injury, and pain were collected. Prolonged parasthesia was the most frequent event reported (40% of patients at 3 hours and 11% at 5 hours), and it occurred most frequently in children under 7 years of age. Soft tissue injury occurred in 14% of children, again occurring most frequently in children under 7 years of age. The lip (not related to the injection site) was the most common site of soft tissue injury. Pain occurred in 20% of children. As with the pediatric clinical trials conducted to support original product approval, no serious adverse events were noted in this prospective study. One case report describing skin necrosis (which resolved) in a 10 year female after receiving an inferior alveolar nerve

⁵ Wrzosek T, Einarson A. Dental care during pregnancy. *Can Fam Phys*; 55, June 2009, 598-9

⁶ Goldenberg R, Culhane J. Preterm birth and periodontal disease. *NEJM*; 355(1), Nov 2006, 1925-7

⁷ Michalowicz B, DiAngelis A, Novac MJ, Buchanan W, Papapanou P, Mitchell D, Curran A, Lupo V, Ferguson J, Bofill J, Matseane S, Dienard A, Rogers T. Examining the safety of dental treatment in pregnant women. *JADA*; 139, June 2008, 685-95

⁸ The Drug and Lactation Database (<http://toxnet.nlm.nih.gov>)

⁹ Guiliani M, Grossi GB, Pilari M, Larjola C, Casparrini G. Could local anesthesia while breastfeeding be harmful to infants? *Jour Ped Gastroenterology*;32(3), Feb 2001, 142-4

¹⁰ AAP Committee on Drugs. The transfer of drugs and other chemicals into human milk. *Pediatrics*;108(3);September 2001

¹¹ Adewumi A, Hall M, Guelmann M, Riley J. The incidence of adverse reactions following 4% septocaine (articaine) in children. *Ped Dent*. 2008 Sep-Oct;30(5):424-8

block with articaine 4% and epinephrine 1:200,000 was noted.¹² The authors theorize that the injection was done intra-arterial and arterial vasospasm occurred from the epinephrine (a labeled warning) and concluded that clinicians should always aspirate with the needle prior to any injection.

CONCLUSIONS

While the Proposed Pregnancy and Lactation Labeling Rule, published May 2008, is in the clearance process, the MHT of the PMHS is structuring the Pregnancy and Nursing Mothers label information in a way that is in the spirit of the Proposed Rule while still complying with current regulations. The goal of this restructuring is to make the pregnancy and lactation sections of labeling a more effective communication tool for clinicians. In addition, PMHS restructured the Pediatric Use labeling to enhance its clinical usefulness.

PMHS LABELING RECOMMENDATIONS

PMHS recommends the following revisions to the Pregnancy, Nursing Mothers, and Pediatric Use subsections in the draft articaine hydrochloride and epinephrine bitartrate injection, solution labeling. In addition, PMHS has revised the Dosage and Administration section of labeling to separate out the adult and pediatric dosing information. Appendix A of this review provides a tracked-changes version of labeling that includes that highlights all changes made.

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OTHER RECOMMENDATIONS

The sponsor stated in Highlights of prescribing information that (b) (4)



PMHS notes that we found no evidence in the literature that adequate and well-controlled clinical studies were conducted in pregnant women using articaine hydrochloride 4% with epinephrine 1:100,000 or articaine hydrochloride 4% with epinephrine 1:200,000.

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/s/

Jeanine Best
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LABELING REVIEWER

Lisa Mathis
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