CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-010

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

13. Patent Information

APPEARS THIS WAY ON ORIGINAL

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

NDA NUMBER
20-971

NAME OF APPLICANT / NDA HOLDER
Deproco, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
Septocaine® — and Septocaine® —

ACTIVE INGREDIENT(S)	STRENGTH(S)
Articaine Hydrochloride 4% Epinephrine (1:100,000 and 1:200,000)	Articaine Hydrochloride 4% with Epinephrine 1:100,000 Articaine Hydrochloride 4% with Epinephrine 1:200,000

DOSAGE FORM
Solution for Injection

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent

d. Name of Patent Owner

Address *(of Patent Owner)*

City/State

ZIP Code	FAX Number *(if available)*
Telephone Number	E-Mail Address *(if available)*

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address *(of agent or representative named in 1.e.)*

City/State

ZIP Code	FAX Number *(if available)*
Telephone Number	E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☐ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☐ No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

	Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☐ Yes	☐ No
2.2	Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☐ No
2.3	If the answer to question **2.2** is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4	Specify the polymorphic form(s) claimed by the patent for which you have the test results described in **2.3**.		
2.5	Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☐ No
2.6	Does the patent claim only an intermediate?	☐ Yes	☐ No
2.7	If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1	Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☐ Yes	☐ No
3.2	Does the patent claim only an intermediate?	☐ Yes	☐ No
3.3	If the patent referenced in **3.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1	Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes	☐ No
4.2	Patent Claim Number *(as listed in the patent)* — Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes	☐ No
4.2a	If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. — Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)*		

5. No Relevant Patents

	For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in manufacture, use, or sale of the drug product.	☒ Yes

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
Wayne H. Matelski/BW	8/31/05

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☐ NDA Applicant/Holder	☒ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Wayne H. Matelski	
Address Arent Fox PLLC, 1050 Connecticut Ave., NW	City/State Washington, DC
ZIP Code 20036	Telephone Number 202-857-6340
FAX Number *(if available)* 202-857-6395	E-Mail Address *(if available)* matelski.wayne@arentfox.com

14. Patent Certification

Septodont
58, rue du Pont de Créteil
94107 Saint-Maur-des-Fossés Cedex
Tél.: +33 (0)1 49 76 70 00
Fax: +33 (0)1 48 85 54 01

PATENT CERTIFICATION

In the opinion and to the best knowledge of Deproco, Inc., there are no patents that claim the drug or drugs on which investigations that are relied upon in this application were conducted or that claim a use of such drug or drugs.

Olivier Schiller
President, Deproco, Inc.

Date : September 8th 2005

EXCLUSIVITY SUMMARY

NDA # 22-010 SUPPL # 000 HFD # 170

Trade Name (articaine HCl 4% and epinephrine 1:200,000)

Generic Name

Applicant Name Deproco, Inc.

Approval Date, If Known March 30, 2006
This NDA has been administratively split from NDA 20-971 as a new dose of Septocaine.

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☐ NO ☒

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

This NDA has been administratively split as a Class 2 complete response NDA from NDA 20-971. The original NDA was pre-PREA, and the requirements for pediatrics were fulfilled for the BPCA from NDA 20-971. Pediatrics are not applicable.

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 20-971 Septocaine

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical

investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☒

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☒

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently

demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

ART 02-001, ART 02-002, ART 02-003, ART 03-001

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☒

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☒

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

ART 02-001, ART 02-002, ART 02-003, ART 03-001

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # 51,721 YES ☒ ! NO ☐
! Explain:

Investigation #2

IND # 51,721 YES ☒ ! NO ☐
! Explain:

Investigation #3

IND # 51,721 YES X

Investigation #4

IND # 51,721 YES X

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

==========

Name of person completing form: Allison Meyer
Title: Regulatory Project Manager
Date: March 30, 2006

Name of Office/Division Director signing form: Bob Rappaport, MD
Title: Director, HFD-170

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : 22-010 **Supplement Type (e.g. SE5):** _____ **Supplement Number:** N000

Stamp Date: 09/30/05 **Action Date:** 03/30/06

HFD 170 **Trade and generic names/dosage form:** Septocaine — (articaine hydrochloride 4% with epinephrine 1:200,000), solution for injection

Applicant: Deproco, Inc. **Therapeutic Class:** 3S/6040100

Indication(s) previously approved: For local, infiltrative, or conductive anesthesia in both simple and complex dental and periodontal procedures.

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): One

Indication #1: _____

Is there a full waiver for this indication (check one)?

- ☐ **Yes: Please proceed to Section A.**

x No: Please check all that apply: x **Partial Waiver** x **Deferred** ____ **Completed**
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:** _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min_____	kg_____	mo._____	yr. 0	Tanner Stage_____
Max_____	kg_____	mo._____	yr. <2 years	Tanner Stage_____

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- x **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

❑ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____	**kg**_____	**mo.**_____	**yr.** 2 years	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.** 16 years	**Tanner Stage**_____

Reason(s) for deferral:

❑ **Products in this class for this indication have been studied/labeled for pediatric population**
❑ **Disease/condition does not exist in children**
❑ **Too few children with disease to study**
❑ **There are safety concerns**
x **Adult studies ready for approval**
❑ **Formulation needed**
Other:_____

Date studies are due (mm/dd/yy): December 31,2008

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____
Allison Meyer, Regulatory Project Manager

cc: **NDA 22-010**
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Is there a full waiver for this indication (check one)?

- ☐ **Yes: Please proceed to Section A.**
- ☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:**_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____
Allison Meyer, Regulatory Project Manager

cc: NDA 22-010
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 10-14-03)

16. Debarment Certification

Please see the cover letter for this sNDA for debarment certification.

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On Original

N-000 C

NEW CORRES

DUPLICATE

Arent Fox
ATTORNEYS AT LAW

Wayne H. Matelski
202.857.6340 DIRECT
202.857.6395 FAX
matelski.wayne@arentfox.com

January 23, 2006

RECEIVED
JAN 26 2006
CDER CDR

VIA FEDERAL EXPRESS

Document Control Room
Division of Anesthesia, Analgesia, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5901-B Ammendale Road (HFD-143)
Beltsville, MD 20705

RECEIVED
JAN 27 2006
CDER Philadelphia DSK DSR I

Re: NDA 22-010
Septocaine® — (Articaine Hydrochloride 4% (40 mg/mL) with Epinephrine 1:200,000 Injection)
Sponsor: Deproco, Inc.

Financial Disclosure by Clinical Investigators

Dear Sir or Madam:

On behalf of Deproco, Inc., the Sponsor of NDA 22-010, and its affiliated manufacturing company, Novocol Pharmaceutical of Canada, Inc., and pursuant to the provisions of 21 C.F.R. Part 54, I am submitting the attached Form FDA 3454 and Forms FDA 3455 covering the clinical investigators who participated in the studies conducted in support of NDA 22-010.

Pursuant to the provisions of 21 C.F.R. § 314.50(l)(3), I hereby certify that I am sending to the FDA's Philadelphia District Office a true copy of this submission.

Should you have any questions, or if we can provide any additional information, please do not hesitate to contact me.

Sincerely,

Wayne H. Matelski
Counsel to and U.S. Agent for Deproco, Inc.
and Novocol Pharmaceutical of Canada, Inc.

Attachments

cc: Allison Meyer (FDA)
Thomas Gardine (FDA/Philadelphia District Office)

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: February 28, 2006.

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

☒ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		
	Please refer to attached list.	

☐ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Wayne H. Matelski	Counsel, U.S. Agent, and Official Correspondent
FIRM / ORGANIZATION	
Deproco, Inc. and Novocol Pharmaceutical of Canada, Inc.	
SIGNATURE: Wayne H. Matelski/BW	DATE: 1/23/06

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

1 Page(s) Withheld

X § 552(b)(4) Trade Secret / Confidential
(b)(6) Personal Privacy

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: February 28, 2006

TO BE COMPLETED BY APPLICANT

The following information concerning _____, who participated as a clinical investigator in the submitted study _____, is submitted in accordance with 21 CFR part 54.

Name of clinical investigator

Name of clinical study

54. The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Please mark the applicable checkboxes.

☐ any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;

☒ any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;

☐ any proprietary interest in the product tested in the covered study held by the clinical investigator;

☐ any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

NAME	TITLE
Wayne H. Matelski	Counsel, U.S. Agent and Official Correspondent
FIRM / ORGANIZATION	
Deproco, Inc. and Novocol Pharmaceutical of Canada, Inc.	
SIGNATURE: Wayne H. Matelski /BW	DATE: 1/23/06

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 4 hours per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14-72
Rockville, MD 20857

Attachment to Form FDA 3455

Item	Amount
Honorarium	
[redacted]	$ 5,277
	$ 5,277
	$ 7,557

Honoraria were provided to each of the Primary Clinical Investigators to compensate them for their participation in the study as Principal Investigators. We believe these honoraria represent the fair market value for the support services provided by the Investigator. These funds were agreed upon before the study began and were wholly independent of any study results

Consulting fee	$ 102,052

The consulting fees were paid to [redacted] to compensate him for his time associated with advising the Company on its drug development plan and interpreting the study results. These fees were paid to [redacted] between May 2001 and December 2005 and were wholly independent of any study results. The Company believes that these fees represent the fair market value for the services provided by [redacted]

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: February 28, 2006

DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

The following information concerning _____, who participated as a clinical investigator in the submitted study _____, is submitted in accordance with 21 CFR part

Name of clinical investigator

Name of clinical study

54. The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Please mark the applicable checkboxes.

☐ any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;

☒ any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;

☐ any proprietary interest in the product tested in the covered study held by the clinical investigator;

☐ any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

NAME	TITLE
Eric Penrose	Director of Quality Assurance and Regulatory Affairs
FIRM / ORGANIZATION: Novocol Pharmaceutical of Canada, Inc.	
SIGNATURE	DATE: 2005-05-30

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 4 hours per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14-72
Rockville, MD 20857

Attachment to Form FDA 3455

Item	Amount
Honorarium	
[ ]	$ 18,982
	$ 18,982
	$ 7,231

Honoraria were provided to each of the Primary Clinical Investigators to compensate them for their participation in the study as Principal Investigators. We believe these honoraria represent the fair market value for the support services provided by the Investigator. These funds were agreed upon before the study began and were wholly independent of any study results

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: February 28, 2006

DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

The following information concerning _____ , who
Name of clinical investigator

participated as a clinical investigator in the submitted study _____
Name of

_____ , is submitted in accordance with 21 CFR
clinical study

54. The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Please mark the applicable checkboxes.

☐ any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;

☒ any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;

☐ any proprietary interest in the product tested in the covered study held by the clinical investigator;

☐ any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

NAME	TITLE
Eric Penrose	Director of Quality Assurance and Regulatory Affairs
FIRM / ORGANIZATION	
Novocol Pharmaceutical of Canada, Inc.	
SIGNATURE	DATE
	1/17/06

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 4 hours per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14-72
Rockville, MD 20857

Attachment to Form FDA 3455

Item	Amount
Honorarium	
[redacted]	$ 14,136
	$ 14,136
	$ 14,136
	$ 12,920

Honoraria were provided to each of the Primary Clinical Investigators to compensate them for their participation in the study as Principal Investigators. We believe these honoraria represent the fair market value for the support services provided by the Investigator. These funds were agreed upon before the study began and were wholly independent of any study results

Study Equipment $ 24,500

The [redacted] was supplied to [redacted] to enable his participation in the study. Study [redacted] effects of the study drugs as recommended by the FDA. [redacted] was the Principal Investigator for this [redacted] study [redacted] This equipment was agreed upon before the study began and was wholly independent of any study results.

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MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: 3/24/06

TO: Allison Meyer, Regulatory Project Manager
Jane Filie, M.D., Clinical Reviewer
Division of Anesthesia, Analgesia, and Rheumatology Drug Products

THROUGH: Constance Lewin, M.D., M.P.H.
Acting Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

FROM: Carolanne Currier. CSO

SUBJECT: Evaluation of Clinical Inspections

NDA: 22-010

APPLICANT: Deproco, Inc.

DRUG: Septocaine (articaine HCl and epinephrine)

THERAPEUTIC CLASSIFICATION: S

INDICATION: Dental anesthesia

CONSULTATION REQUEST DATE: 2/7/06

PDUFA DATE: 3/31/06

I. BACKGROUND:

NDA 22-010 is an application for a new formulation of the drug product Septocaine – a combination of articaine and epinephrine. Articaine 4% with epinephrine 1:100,000 is currently marketed in the US (NDA 20-971). The new formulation is for articaine 4% with epinephrine 1:200,000. Because the NDA involves a new formulation of a marketed combination of two well-studied products, the Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP) initially decided that inspections of the

clinical studies for this NDA were not necessary. However, upon receiving the financial disclosure forms for the clinical investigators, DAARP noticed that three investigators at different institutions [redacted] reported they had received significant sums of money or large pieces of equipment from the sponsor. DAARP also noted that the efficacy reported from each trial was extremely variable across these sites ([redacted] respectively), and that the success rate appeared to correlate with the amount of money or equipment each investigator received. Inspection of the sponsor and the three investigators' trials was requested to determine if financial incentives could have introduced any bias into the study results.

The three investigators performed studies with three protocols that were identified as important to the approval of the NDA: [redacted]

It should be noted that although an inspection of the sponsor, Deproco, Inc., New Castle, Delaware, was requested, it was discovered that all records relating to their clinical trials were kept at their facility in Canada. Due to the inability to get the foreign inspection scheduled and conducted before the PDUFA date, the sponsor inspection was cancelled. The remainder of this Summary relates solely to the clinical investigator inspections.

II. RESULTS (by protocol/site):

Investigator	City, State	Protocol	Insp. Date	Date EIR Received	Class.
[redacted]				Pending	Pending (NAI)
[redacted]				Pending	Pending (NAI)
[redacted]				Pending	Pending (NAI)

Key to Classifications
NAI = No deviation from regulations.
VAI-No Response Requested= Deviations(s) from regulations.
VAI-Response Requested = Deviation(s) form regulations. See specific comments below for data acceptability
OAI = Significant deviations for regulations.
Classifications in parenthesis are the recommended classification by the inspecting field office.

A. Protocol # [redacted]

1. [redacted]

a. What was inspected: [redacted] enrolled [redacted] in protocol [redacted] All subjects signed the informed consent form before entering the study. Study records for 7 of the [redacted] were reviewed in-depth during the inspection. There were no discrepancies between the data recorded on case report forms (CRFs - which in this case were the source documents) and the data listings provided to FDA. There was no evidence of under-reporting of adverse events.

There was no evidence found that [redacted] had introduced bias into the study results. [redacted] wrote the protocols and supervised the studies, but other dentists and periodontists did the actual procedures and data collection.

b. Limitations of inspection: None

c. General observations/commentary: The EIR for this inspection site has not been received to date. Observations noted above are based on email communications from the FDA field investigator who conducted the on-site inspection. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

d. Data acceptability: The study appears to have been conducted properly with no deviations from FDA regulations. From the records reviewed, it appears the data are acceptable to use to support the NDA.

2. [redacted]

a. What was inspected: [redacted] enrolled [redacted] n protocol [redacted] and all [redacted] completed the study. All subjects signed the informed consent form before entering the study. Study records for 10 of the [redacted] were reviewed in-depth during the inspection. There were no discrepancies between the data recorded on case report forms (which in this case were the source documents) and the data listings provided to FDA. There was no evidence of under-reporting of adverse events.

There was no evidence found that [redacted] had introduced bias into the study results. [redacted] supervised the studies, but the sub-investigator performed the study procedures and the research coordinator recorded the data onto the CRFs.

b. Limitations of inspection: None

c. General observations/commentary: The EIR for this inspection site has not been received to date. Observations noted above are based on verbal and email communications from the FDA field investigator who conducted the on-site inspection. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

d. Data acceptability: The study appears to have been conducted properly with no deviations from FDA regulations. From the records reviewed, it appears the data are acceptable to use to support the NDA.

3. [redacted]

a. What was inspected: [redacted] enrolled [redacted] in protocol [redacted] [redacted] completed the study. [redacted] subjects signed the informed consent form before entering the study. Study records for 6 of the [redacted] subjects were reviewed in-depth during the inspection. There were no discrepancies between the data recorded on case report forms (which in this case were the source documents) and the data listings provided to FDA. There was no evidence of under-reporting of adverse events.

There was no evidence found that [redacted] had introduced bias into the study results. [redacted] supervised the trial, but the study procedures were performed by other dentists, and assistants recorded data on CRFs. The dentists and the assistants were not [redacted]

b. Limitations of inspection: None

c. General observations/commentary: The EIR for this inspection site has not been received to date. Observations noted above are based on email communications from the FDA field investigator who conducted the on-site inspection. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

d. Data acceptability: The study appears to have been conducted properly with no deviations from FDA regulations. From the records reviewed, it appears the data are acceptable to use to support the NDA.

A. Protocol # ,

1. ———————————

a. What was inspected: ——— enrolled ——— n protocol ——— All subjects signed the informed consent form before entering the study. Study records for 5 of the ——— /ere reviewed in-depth during the inspection. There were no discrepancies between the data recorded on case report forms (CRFs - which in this case were the source documents) and the data listings provided to FDA. There was no evidence of under-reporting of adverse events.

There was no evidence found that ——— had introduced bias into the study results. ———wrote the protocols and supervised the studies, but other dentists and periodontists did the actual procedures and data collection.

b. Limitations of inspection: None

c. General observations/commentary: The EIR for this inspection site has not been received to date. Observations noted above are based on email communications from the FDA field investigator who conducted the on-site inspection. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

d. Data acceptability: The study appears to have been conducted properly with no deviations from FDA regulations. From the records reviewed, it appears the data are acceptable to use to support the NDA.

2. ———————————

a. What was inspected: ——— enrolled ——— s in protocol ——— ——— subjects completed the study. All subjects signed the informed consent form before entering the study. Study records for 10 of the ——— were reviewed in-depth during the inspection. There were no discrepancies between the data recorded on case report forms (which in this case were the source documents) and the data listings provided to FDA. There was no evidence of under-reporting of adverse events.

There was no evidence found that [redacted] had introduced bias into the study results. [redacted] supervised the studies, but the sub-investigator performed the study procedures and the research coordinator recorded the data onto the CRFs.

b. Limitations of inspection: None

c. General observations/commentary: The EIR for this inspection site has not been received to date. Observations noted above are based on verbal and email communications from the FDA field investigator who conducted the on-site inspection. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

d. Data acceptability: The study appears to have been conducted properly with no deviations from FDA regulations. From the records reviewed, it appears the data are acceptable to use to support the NDA.

3. [redacted]

a. What was inspected: [redacted] enrolled [redacted] in protocol [redacted]. All subjects signed the informed consent form before entering the study. Study records for 6 of the [redacted] were reviewed in-depth during the inspection. There were no discrepancies between the data recorded on case report forms (which in this case were the source documents) and the data listings provided to FDA. There was no evidence of under-reporting of adverse events.

There was no evidence that [redacted] had introduced bias into the study results. [redacted] supervised the trial, but the study procedures were performed by other dentists, and assistants recorded data on CRFs. The dentists and the assistants were [redacted]

b. Limitations of inspection: None

c. General observations/commentary: The EIR for this inspection site has not been received to date. Observations noted above are based on email communications from the FDA field investigator who conducted the on-site inspection. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

d. Data acceptability: The study appears to have been conducted properly with no deviations from FDA regulations. From the records reviewed, it appears the data are acceptable to use to support the NDA.

A. Protocol # [redacted]

1. [redacted]

a. What was inspected: ——— enrolled ——— in protocol ———. All subjects signed the informed consent form before entering the study. Study records for 6 of the ——— were reviewed in-depth during the inspection. There were no discrepancies between the data recorded on case report forms (which in this case were the source documents) and the data listings provided to FDA. There was no evidence of under-reporting of adverse events.

There was no evidence found that ——— had introduced bias into the study results. ——— wrote the protocols and supervised the studies, but other dentists and periodontists did the actual procedures and data collection.

b. Limitations of inspection: None

c. General observations/commentary: The EIR for this inspection site has not been received to date. Observations noted above are based on email communications from the FDA field investigator who conducted the on-site inspection. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

d. Data acceptability: The study appears to have been conducted properly with no deviations from FDA regulations. From the records reviewed, it appears the data are acceptable to use to support the NDA.

2. ———

a. What was inspected: ——— enrolled ——— protocol ——— and ——— ompleted the study. All subjects signed the informed consent form before entering the study. Study records for 7 of the ——— were reviewed in-depth during the inspection. There were no discrepancies between the data recorded on case report forms (which in this case were the source documents) and the data listings provided to FDA. There was no evidence of under-reporting of adverse events.

There was no evidence found that ——— had introduced bias into the study results. ——— supervised the studies, but the sub-investigator performed the study procedures and the research coordinator recorded the data onto the CRFs.

b. Limitations of inspection: None

c. General observations/commentary: The EIR for this inspection site has not been received to date. Observations noted above are based on verbal and email communications from the FDA field investigator who conducted the on-site inspection. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

d. Data acceptability: The study appears to have been conducted properly with no deviations from FDA regulations. From the records reviewed, it appears the data are acceptable to use to support the NDA.

3. [redacted]

a. What was inspected: [redacted] enrolled [redacted] in protocol [redacted] [redacted] completed the study. All subjects signed the informed consent form before entering the study. Study records for 4 of the [redacted] were reviewed in-depth during the inspection. There were no discrepancies between the data recorded on case report forms (which in this case were the source documents) and the data listings provided to FDA. There was no evidence of under-reporting of adverse events.

There was no evidence found that [redacted] had introduced bias into the study results. The actual study procedures were performed by other dentists and dental assistants recorded data on CRFs. The dentists and the assistants were [redacted]

b. Limitations of inspection: None

c. General observations/commentary: The EIR for this inspection site has not been received to date. Observations noted above are based on verbal and email communications from the FDA field investigator who conducted the on-site inspection. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

d. Data acceptability: The study appears to have been conducted properly with no deviations from FDA regulations. From the records reviewed, it appears the data are acceptable to use to support the NDA.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

As mentioned above, the findings noted from inspection of the [redacted] study sites are from verbal and email conversations with the FDA field investigators who conducted the inspections. The EIRs have not yet been received by DSI. The field investigators have indicated that there were no problems found in the conduct of any of the three studies, nor was there any evidence to suggest that the clinical investigator had influenced the data or the outcome of the trials.

Based on the preliminary reports from the field investigators, it appears that the data from all three studies could be used to support an approval decision for the NDA. If any information to the contrary is revealed upon the receipt and final review of the EIRs from the inspections, DAARP will be notified immediately, and an addendum to this Summary will be generated.

{See appended electronic signature page}

Carolanne Currier, CSO

CONCURRENCE:

Supervisory comments

{See appended electronic signature page}

Constance Lewin, M.D., M.P.H.
Acting Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Carolanne Currier
3/27/2006 12:37:12 PM
MANGMNT ANALYST

Change made.

Constance Lewin
3/27/2006 12:40:49 PM
MEDICAL OFFICER

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

Memorandum

Date: March 9, 2006

To: Allison Meyer, Regulatory Project Manager
Division of Anesthesia, Analgesia, and Rheumatology Products

From: Michelle Safarik, PA-C, Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications

Subject: NDA 22-010
DDMAC labeling comments for Septocaine — and Septocaine — (articaine hydrochloride 4% (40 mg/mL) with epinephrine 1:100,000 or 1:200,000 injection)

Per your consult request dated March 7, 2006, DDMAC has reviewed the proposed product labeling (PI) and proposed carton and cartridge labeling for Septocaine. While this supplement provides for a new dosage strength of Septocaine (Septocaine —), DDMAC has reviewed the entire label.

PI

Clinical Pharmacology

Pharmacokinetics

Metabolism

1. "Articaine HCl is rapidly metabolized..."

   Would it be possible to provide context for "rapid"?

Special Populations

1. —

   Would it be possible to provide context for "— ' and "' — '?

2. "

Is this phrase accurate? If not, we recommend deletion.

Pharmacodynamics

1. "...however, in healthy adults it does not appear to be associated with marked increases in blood pressure or heart rate..."

   Is this phrase accurate? If not, we recommend deletion.

Clinical Trials

1. Table 1 in the current Septocaine PI presents a summary of VAS pain scores for simple and complex procedures. Is it appropriate to include such a table in this proposed PI as well?

2. "Four randomized, double-blind, active-controlled studies were performed comparing Septocaine ®versus Septocaine ®...

   Is this paragraph describing the efficacy of Septocaine accurate and supported by substantial evidence to be included in labeling? If not, we recommend deletion. If so, we recommend placing the pharmacokinetic and risk information statements in this paragraph into the appropriate sections in the proposed PI.

Indications and Usage

1. "Septocaine® improve visualization of the surgical field."

   Are the studies described in the **Clinical Trials** section of the proposed PI considered substantial evidence to support these two proposed indications? If not, we recommend deletion.

2. We recommend including a statement such as, "Septocaine® is indicated for use in patients 4 years of age and older" for consistency with the LidoSite PI and other PI's which have age limitations to their safe and effective use.

Precautions

General

1. "...which may lead to atrioventricular block, ventricular arrhythmias, and cardiac arrest, possibly resulting in fatalities" (emphasis added).

   The current Septocaine PI states, "... ——— resulting in fatalities" (emphasis added). "Possibly" is speculative and minimizes the risks of Septocaine use, whereas ——— is more definitive. Which word is correct?

Pediatric Use

1. "No unusual adverse events were noted in these patients."

   Is this statement accurate? If not, we recommend deletion.

Geriatric Use

1. Would it be possible to provide context for "administered safely" and "safely administered?" Does that mean administered without adverse events?

Adverse Reactions

1. "Reactions to Septocaine® are characteristic of those associated with other amide-type local anesthetics."

   Although this statement appears in the current Septocaine PI, it is promotional in tone and minimizes the risks associated with use of Septocaine; we recommend deletion.

Carton Labeling

1. "Store —25°C (77°F)."

   For consistency with the **How Supplied** section of the proposed PI, we recommend including the phrase, "with brief excursions permitted between 15°C and 30°C (59°F-96°F) (see USP controlled room temperature)."

2. "FOR INFILTRATION AND NERVE BLOCK ANESTHESIA" and "INDICATIONS...This drug product is indicated for local, infiltrative, or conductive anesthesia in both simple and complex dental ——— procedures" (original emphasis).

Because these statements describe the drug's use/indication, they make representations about the product and therefore require balancing risk information. Alternatively, the sponsor may choose to delete these statements.

3. "...; [redacted]: 1.7mL."

   For consistency with the **How Supplied** section of the PI, we recommend deletion of the word [redacted]

Cartridge Labeling

We have reviewed the proposed cartridge labeling and have no comments at this time.

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Michelle Safarik
3/9/2006 01:44:26 PM
DDMAC REVIEWER

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
NDA 22-010	Efficacy Supplement Type SE-	Supplement Number	
Drug: articaine HCL 4% with epinephrine 1:200,000		Applicant: Deproco, Inc.	
RPM: Allison Meyer		HFD-170	Phone # 301-796-1258

Application Type: ( ) 505(b)(1) **(x)** 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.) **If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.** **(x)** Confirmed and/or corrected	Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)): NDA 20-971, Septocaine®

❖ Application Classifications:	
• Review priority	**(x)** Standard ( ) Priority
• Chem class (NDAs only)	4S
• Other (e.g., orphan, OTC)	
❖ User Fee Goal Dates	March 31, 2006
❖ Special programs (indicate all that apply)	**(x)** None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review ( ) CMA Pilot 1 ( ) CMA Pilot 2
❖ User Fee Information	
• User Fee	**(x)** Paid UF ID number
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other (specify)
• User Fee exception	( ) Orphan designation **(x)** No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) ( ) Other (specify)
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes **(x)** No

• This application is on the AIP	( ) Yes (x) No
• Exception for review (Center Director's memo)	
• OC clearance for approval	
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.	(x) Verified
❖ Patent	
• Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	(x) Verified
• Patent certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) (x) Verified 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	
• [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next box below (Exclusivity)).*	( ) N/A (no paragraph IV certification) ( ) Verified
• [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. Answer the following questions for each paragraph IV certification: (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))). *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).* (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**No**," continue with question (3).* (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?	( ) Yes ( ) No ( ) Yes ( ) No ( ) Yes ( ) No

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))). *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.* (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**No**," continue with question (5).* (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.*	( ) Yes ( ) No ( ) Yes ( ) No
❖ Exclusivity (approvals only)	
• Exclusivity summary • Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)	yes
• Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	( ) Yes, Application #_____ **(x)** No
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	yes

General Information	
❖ Actions	
• Proposed action	**(x)** AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	
• Status of advertising (approvals only)	**(x)** Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	( ) Yes **(x)** Not applicable
• Indicate what types (if any) of information dissemination are anticipated	**(x)** None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	Yes
• Most recent applicant-proposed labeling	Yes
• Original applicant-proposed labeling	Yes
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	Yes
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	yes
• Applicant proposed	
• Reviews	yes
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	
• Documentation of discussions and/or agreements relating to post-marketing commitments	
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	Yes
❖ Memoranda and Telecons	yes
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	
• Pre-NDA meeting (indicate date)	
• Pre-Approval Safety Conference (indicate date; approvals only)	
• Other	
❖ Advisory Committee Meeting	
• Date of Meeting	
• 48-hour alert	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	

Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	Yes
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	Yes
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	Yes
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	Yes
❖ Risk Management Plan review(s) *(indicate date/location if incorporated in another rev)*	
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	Yes
❖ Demographic Worksheet *(NME approvals only)*	
❖ Statistical review(s) *(indicate date for each review)*	Yes
❖ Biopharmaceutical review(s) *(indicate date for each review)*	Yes
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	Yes
• Bioequivalence studies	
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	yes
• Review & FONSI *(indicate date of review)*	
• Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Microbiology (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	yes
❖ Facilities inspection (provide EER report)	Date completed: **(x)** Acceptable **( )** Withhold recommendation
❖ Methods validation	**()** Completed **(x)** Requested **( )** Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	
❖ Nonclinical inspection review summary	
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	
❖ CAC/ECAC report	

Appendix A to NDA/Efficacy Supplement Action Package Checklist

An application is likely to be a 505(b)(2) application if:

(1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
(2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
(4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

FDA CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF ANESTHESIA, ANALGESIA AND RHEUMATOLOGY PRODUCTS

DIVISION DIRECTOR REVIEW AND BASIS FOR APPROVAL ACTION

DATE:	March 30, 2006
DRUG:	Articaine HCl 4% with Epinephrine 1:200,000
NDA:	22-010
SPONSOR:	Deproco, Inc.
INDICATION:	for local, infiltrative or conductive anesthesia in both simple and complex dental ——— procedures

Deproco, Inc. submitted the original NDA for Articaine HCl in 1998. That submission included labeling for two formulations, one with epinephrine 1:100,000 and the other with epinephrine 1:200,000. However, all of the clinical trials included in the application were performed with the epinephrine 1:100,000 formulation, thus only that formulation was approved. In the approvable letter for the 1:200,000 formulation, documentation was requested that would demonstrate adequate efficacy of this formulation, a clinical benefit to support the addition of epinephrine to articaine, and a clinical difference for the 1:200,000 formulation compared to the approved formulation. The sponsor submitted their response to the approvable letter on September 30, 2005.

The clinical studies in this application were reviewed by Jane Filie, M.D. A statistical review of those studies was provided by Youngman Kim, Ph.D. The CMC data was reviewed by William M. Adams, Ph.D. The pharmacology/toxicology portion of the submission was reviewed by Mamata De, Ph.D. The clinical pharmacology and biopharmaceutics portion of the application was reviewed by Suresh Doddapanneni, Ph.D. Arthur Simone, M.D., Ph.D. provided a supervisory review of the application. Consultations on this application were provided by Fred Hyman, D.D.S., M.P.H. of the Division of Dermatology and Dental Products, as well as by the Office of Drug Safety and the Division of Drug Marketing, Advertising and Communications.

The sponsor submitted four clinical studies in support of the application. These studies included a pharmacokinetic/safety study and three efficacy trials. The three efficacy trials have been reviewed in detail by Drs. Filie, Kim and Simone. I will briefly summarize the results of those studies.

Studies ART 02-001 (001) and ART 02-002 (002) were of identical design, except that Study 001 evaluated inferior alveolar nerve block anesthesia and Study 002 evaluated maxillary infiltration anesthesia. Both studies compared the 1:100,000 and 1:200,000 epinephrine formulations to each other, as well as to an articaine without epinephrine formulation. The primary outcome measure was the "success rate for achieving profound anesthesia within 10 minutes of test drug administration" using a Electrical Pulp Testing (EPT) as a surrogate for a painful dental procedure. Treatment success was defined as a subject having three consecutive EPT values indicating complete anesthesia. Secondary outcome measures evaluated onset and duration of anesthesia.

As per the clinical teams' reviews, both studies clearly demonstrated that there were no differences in the success rates for the two epinephrine-containing formulations, and that each of those formulations had a statistically significantly greater success rate compared to the articaine without epinephrine formulation. Although the success rates varied considerably among study sites and were generally lower than would be expected based on the dental literature in Study 001, these findings were likely related to technical performance and not to the efficacy of the drug products. The fact that the 1:200,000 formulation was found to be non-inferior to the approved formulation in both studies should support the efficacy of this product in any case. The studies also demonstrated that the two formulations have similar pharmacodynamics in terms of onset and duration of anesthesia. Of note, both of the epinephrine-containing formulations provided a greater duration of anesthesia than the articaine-alone formulation.

Study ART 02-003 (003) was a comparison of the hemostatic efficacy of the two epinephrine-containing formulations when administered intraorally to induce maxillary anesthesia required for periodontal surgery. While there were some flaws in the study design, all of the clinical reviewers agreed that this study demonstrated that the 1:100,000 epinephrine formulation provided better surgical field visualization than the 1:200,000 epinephrine formulation. This conclusion was confirmed even after a conservative sensitivity analysis performed by Dr. Filie.

The safety profile of the 1:200,000 epinephrine formulation was found to be essentially the same as that of the approved 1:100,000 epinephrine formulation.

No clinically relevant concerns were raised by the pharmacology/toxicology or clinical pharmacology/biopharmaceutics reviews. The CMC reviewer found no drug quality concerns.

Discussion:

I concur with the review team that the sponsor has demonstrated that articaine HCl with epinephrine 1:200,000 is safe and effective when used according to the product labeling. They have also fulfilled the fixed-drug combination rule by demonstrating that the addition of epinephrine to articaine prolongs anesthesia. Finally they have demonstrated that the original formulation provides an advantage over the new formulation by providing better surgical field visualization due to improved hemostasis and, thus, marketing of both products is justified.

Action: Approval

Bob A. Rappaport, M.D.
Director
Division of Anesthesia, Analgesia and Rheumatology Products
Office of Drug Evaluation II, CDER, FDA

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Bob Rappaport
3/30/2006 03:17:20 PM
MEDICAL OFFICER

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PID #: D060063-A060099

DATE: March 29, 2006

FROM: Andrea Feight D.M.D., M.P.H., Epidemiologist
Division of Surveillance, Research and Communication Support
Office of Drug Safety

THROUGH: Toni Piazza-Hepp, Pharm.D., Acting Director
Division of Surveillance, Research and Communication Support
Office of Drug Safety

TO: Lauren Lee, Pharm.D., Safety Evaluator Team Leader
Martin Pollock, Pharm.D., Safety Evaluator
Division of Drug Risk Evaluation
Office of Drug Safety

SUBJECT: Articaine and Lidocaine - Drug utilization and literature review of paresthesia incidence
NDA# 22-010 Septocaine® — (Articaine Hydrochloride 4% with Epinephrine 1:200,000 Injection)

****This document contains proprietary drug use data which cannot be shared outside of FDA without clearance from the data vendors obtained through the Office of Drug Safety.****

BACKGROUND

In correspondence dated January 27, 2006, the Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP) requested a consult from the Office of Drug Safety (ODS), Division of Drug Risk Evaluation (DDRE), to review spontaneous adverse event reports for Septocaine® (articaine hydrochloride 4% with epinephrine 1:100,000 injection) as reported to the Adverse Event Reporting System (AERS). DAARP also requested a comparison of the adverse event reports for paresthesias and prolonged anesthesia (numbness effect) between lidocaine and articaine. In order to support this request, DDRE requested on March 3 that the Division of Surveillance, Research, and Communication Support (DSRCS) provide drug utilization information, a literature review on paresthesias associated with lidocaine and articaine, and dental epidemiology expertise.

This consult does not attempt to duplicate information contained in the February 23 consult from the Division of Dermatologic and Dental Drug Products regarding the review of the clinical trials for safety and efficacy. That document contains some regulatory background and an excellent clinical dental review of the important factors in comparing the efficacy and safety of Septocaine® — with Septocaine® —

Articaine is a local anesthetic for both dental and periodontal procedures that was introduced to the dental market in Germany in 1976 and subsequently marketed throughout Europe. It was made available in Canada in 1983, and since then its use has steadily grown. Septocaine®, containing articaine hydrochloride 4% with epinephrine 1:100,000, gained U.S. approval on April 3, 2000 under NDA# 20-971. The current NDA is for a local anesthetic containing articaine hydrochloride 4% with epinephrine 1:200,000 that will be co-marketed to provide dental practitioners the choice of the same anesthetic agent with a lower concentration of epinephrine.

The purpose of this review was to estimate the utilization of lidocaine and articaine in the U.S. population and thereby provide the denominator to establish the reporting rate of adverse events with these products.

METHODS

For this report, we examined drug utilization data for lidocaine and articaine from four different sources: (1) IMS Health, National Sales Perspectives™, (2) sales data from Septodont, Inc., Kodak (Cooke-Waite), and Dentsply Pharmaceutical for the year 2005, (3) a search of the published medical literature, and (4) a Google search. We also reviewed the medical literature in an attempt to obtain the incidence rate of paresthesia following the administration of various local dental anesthetics, with a focus on lidocaine and articaine. We performed a search of the medical literature using PubMed and reviewed articles on paresthesia associated with local anesthetics. We performed a literature search in Medline using PubMed for the terms 'paresthesia', 'articaine', 'Septocaine', 'Ultracaine', 'Carticaine', 'lidocaine', and 'local anesthetic'. An identical search was repeated utilizing Google. We reviewed both original publications as well as review articles.

RESULTS

I. DRUG UTILIZATION

IMS Health, National Sales Perspectives™

We accessed IMS Health, National Sales Perspectives™, which is the sole database currently licensed by the FDA that contains data for the various lidocaine and articaine products. However, the sales data are entirely insufficient for providing any information about the utilization of these agents in the dental setting. A specific 'dental' designation was found for only ——————————, although it is clear that many

more of the products included on the list are utilized in the dental setting and should have carried a 'dental' designation. Furthermore, the sales data did not indicate the channels of distribution for these products. Typically, dental anesthetic cartridges (or carpules) are sold in boxes by the case through medical or dental warehouses and dental supply houses. A characterization of product delivery into the dental setting is not available to the Agency. Hence, IMS Health's National Sales Perspectives™ data were inadequate for characterizing the sales and distribution of articaine and lidocaine, and we were not able to use them as a surrogate for drug utilization.

Sales data - Septodont, Inc., Kodak (Cooke-Waite), and Dentsply Pharmaceutical
Bulk sales data figures were obtained in confidence from Septodont, Inc., Kodak (Cooke-Waite), and Dentsply Pharmaceutical for the year 2005 (Table 1). We have anectdotal information that the combined sales from these three manufacturers reflect ——— of total U.S. sales for lidocaine and —— of sales for articaine. Utilizing these figures, we estimated that during 2005 articaine was sold at approximately —, the rate of lidocaine.

Table 1. Estimated Number of Individual Dental Anesthetic Cartridges Sold by Manufacturers to Warehouses and Dental Supply Houses during 2005*

Products	Number of Cartridges
Total Lidocaine	
Lidocaine HCl 2% Plain	
Lidocaine HCl 2% and Epinephrine 1:100,000	
Lidocaine HCl 2% and Epinephrine 1:50,000	
Articaine HCl 4% and Epinephrine 1:100,000	
TOTAL	
% estimate that articaine is used	

*CONFIDENTIAL COMMERCIAL INFORMATION. NOT TO BE RELEASED OUTSIDE FDA.
These estimates are based on the assumption that the lidocaine figures represent —— of the lidocaine market and that the articaine figures represent —— of the articaine market.

Literature Review

The literature provides little information regarding local dental anesthetic utilization. It has been estimated that local dental anesthetics are administered 300 million times annually.[1] A study published in 2000 estimated that on the national level, lidocaine was used in 62% of the dental anesthetic procedures and that approximately 161 million carpules of local dental anesthetics were sold in 1999.[2] These estimates pre-dated the availability of articaine in the U.S.

[1] Lustig JP, Zusman SP. Immediate complications of local anesthetic administered to 1,007 consecutive patients. J Am Dent Assoc. 1999 Apr;130(4):496-9.
[2] Pogrel MA, Thamby SRI. Permanent nerve involvement resulting from inferior alveolar nerve blocks. J Am Dent Assoc. 2000 Jul;131(7):901-7. Erratum in: J Am Dent Assoc 2000 Oct;131(10):1418.

In 2004, there were approximately 135,000 dentists in the U.S. practicing general dentistry or a dental specialty in which local dental anesthetics would be routinely used.[3]

II. PARESTHESIA ASSOCIATED WITH LOCAL DENTAL ANESTHESIA

Literature Review

There are a few published studies describing the efficacy of 4% articaine with 1:100,000 epinephrine, as compared to 2% lidocaine with 1:100,000 epinephrine. However, there is a paucity of literature on the incidence rates of paresthesia following the administration of the various local dental anesthetics. Paresthesia is generally thought to be the result of a traumatic injury to the nerve and can occur following intraoral surgeries or following local anesthetic injection. It is now conjectured that paresthesia is due to both the mechanical and toxic effects of local anesthetic administration.

In a 21-year retrospective study by Haas et al., the observed frequency of paresthesia following local anesthetic administration of articaine or prilocaine was significantly greater than the expected frequency for these agents.[4] The authors examined the pattern and numbers of reported cases of paresthesia in Ontario as recorded by Ontario's Professional Liability Program from 1973 through 1993. The trend in paresthesias over this period turned sharply upward following 1983, when articaine was first marketed in Canada. All 143 reports evaluated involved the mandibular arch. There were no significant differences in age, gender, or gauge of needle used. In 1993 alone, there were 14 reports of paresthesia not associated with surgery, of which 10 cases were administered articaine and 4 cases prilocaine. The estimated incidence of paresthesia following use of 4% articaine for mandibular block was 1:785,000 injections. The authors postulate that the increased concentration of both articaine and prilocaine (4%), as compared to lidocaine (2%), may be responsible for an increased toxic effect. They concluded that the study results were consistent with unconfirmed suggestions that local anesthetic formulations may have the potential for mild neurotoxicity.

In a prospective study in the U.S. that preceded the availability of articaine, patients who were referred to a tertiary care center with permanent paresthesia of the inferior alveolar nerves, lingual nerves, or both following inferior alveolar nerve block were studied.[5] The authors estimated that the incidence for this complication was between 1:26,762 and 1:160,571. Of the local anesthetic agents administered, prilocaine was found to be more frequently associated with cases of nerve injury.

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[3] Bureau of Labor Statistics, U.S. Department of Labor, Career Guide to Industries, 2006-07 Edition, Health Care, on the Internet at http://www.bls.gov/oco/cg/cgs035.htm (visited March 17, 2006)

[4] Haas DA, Lennon D. A 21 year retrospective study of reports of paresthesia following local anesthetic administration. J Can Dent Assoc. 1995 Apr;61(4):319-20, 323-6, 329-30.

[5] Pogrel MA, Thamby SRI. Permanent nerve involvement resulting from inferior alveolar nerve blocks. J Am Dent Assoc. 2000 Jul;131(7):901-7. Erratum in: J Am Dent Assoc 2000 Oct;131(10):1418.

More recently, a relationship between inferior alveolar nerve block injection with articaine and prolonged paresthesia was described.[6] Due to the uncertainty regarding the potential neurotoxic effects of the higher concentrated local anesthetics on the inferior alveolar and lingual nerves, it was suggested that use of 4% articaine should be avoided for mandibular block until more information becomes available.[7] Furthermore, it was suggested that practitioners should reduce the dosage of local anesthetics to the minimum amount required for effective anesthesia and employ the most atraumatic injection technique possible for inferior alveolar and lingual nerve block injections.[8]

LIMITATIONS

Findings from this consult should be interpreted in the context of the known limitations of the databases used. Currently, the data resources available to the Agency do not capture the utilization of dental drug products such as lidocaine and articaine used in the clinical dental setting. Moreover, sales data suggest that dental use represents only a small portion of total product use, and the sales data appear to underreport the specific dental cartridge dosage form. Therefore, the lack of data on local dental anesthetic utilization is a major limitation of the current analysis.

We acknowledge that the anecdotal sales data obtained in confidence from Septodont, Inc., Kodak (Cooke-Waite), and Dentsply Pharmaceutical cannot provide us with the total number of carpules purchased by practitioners and ultimately utilized in patient care. Nonetheless, these data can shed some light on the proportional utilization of articaine relative to lidocaine.

CONCLUSIONS

Utilizing available sales data, we estimated that during 2005 articaine was sold at approximately —— the rate of lidocaine. The literature provided little information regarding local dental anesthetic utilization. Thus, in the absence of valid drug utilization information for articaine and lidocaine for dentistry, it is not possible to develop a reporting rate of paresthesia for the AERS cases nor to compare the relative rates of reporting for paresthesia between articaine and lidocaine. Results of a literature review examining incidence of paresthesia associated with dental analgesia is also presented in this consult.

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[6]van Eeden SP, Patel MF. Re: prolonged paraesthesia following inferior alveolar nerve block using articaine. Br J Oral Maxillofac Surg. 2002 Dec;40(6):519-20.
[7]Petersen J. Pass on 4% Articaine for Mandibular Foramen Block. J Dent. 2003; 107(8): 36-37.
[8]Budenz AW. Local anesthetics in dentistry: then and now. J Calif Dent Assoc. 2003 May;31(5):388-96.

Copies:

NDA 22-010 / 20971
HFD-170: Rappaport/Hertz/Simone/Filie/Myer
HFD-540: Hyman/Kelsey
HFD-440: Avigan//Johann-Liang//Pollock/Lee/Birdsong
HFD-410: Piazza-Hepp/Kaplan/Feight/Governale/Pamer/Mills

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 22-010 Supplement # Efficacy Supplement Type SE-

Trade Name: Septocaine
Established Name: Articaine Hydrochloride 4% (40 mg/mL) with Epinephrine 1:200,000 Injection
History: This NDA is being submitted as a new dose, previously given an approveable action, via teleconference, at the time of approval of NDA 20-971, Septocaine. The NDA has been administratively split from NDA 20-971 because there was no action letter associated with this dose.
Applicant: Deproco
Agent for Applicant: Arent Fox, Wayne Matelski

Date of Application: September 29, 2005
Date of Receipt: September 30, 2005
Date clock started after UN:
Date of Filing Meeting: November 15, 2005
Filing Date: November 29, 2005
Action Goal Date (optional): March 30, 2006 User Fee Goal Date: March 30, 2006

Indication(s) requested: dental anesthetic for infiltration and nerve block anesthesia

Type of Original NDA: (b)(1) ☐ (b)(2) ☒
OR
Type of Supplement: (b)(1) ☐ (b)(2) ☐

NOTE:

(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2), complete Appendix B.

(2) If the application is a supplement to an NDA, please indicate whether the NDA is a (b)(1) or a (b)(2) application:

☐ NDA is a (b)(1) application OR ☒ NDA is a (b)(2) application

Therapeutic Classification: S ☒ P ☐
Resubmission after withdrawal? ☐ Resubmission after refuse to file? ☐
Chemical Classification (1,2,3 etc.): 1
Other (orphan, OTC, etc.):

Form 3397 (User Fee Cover Sheet) submitted: YES ☐ NO ☒

User Fee Status: Paid ☒ Exempt (orphan, government) ☐
Waived (e.g., small business, public health) ☐

NOTE: *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication*

for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the user fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in an approved (b)(1) or (b)(2) application? YES ☐ NO ☒
  If yes, explain:

- Does another drug have orphan drug exclusivity for the same indication? YES ☐ NO ☒

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES ☐ NO ☒

  If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES ☐ NO ☒

  If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES ☐ NO ☐

- Does the submission contain an accurate comprehensive index? YES ☒ NO ☐

  If no, explain:

- Was form 356h included with an authorized signature? YES ☒ NO ☐
  If foreign applicant, both the applicant and the U.S. agent must sign.

- Is the submission complete as required under 21 CFR 314.50? YES ☒ NO ☐

  If no, explain:

- If an electronic NDA, does it follow the Guidance? N/A ☒ YES ☐ NO ☐
  If an electronic NDA, all forms and certifications must be in paper and require a signature.

  Which parts of the application were submitted in electronic format?

  Additional comments:

- If an electronic NDA in Common Technical Document format, does it follow the CTD guidance? N/A ☒ YES ☐ NO ☐

- Is it an electronic CTD (eCTD)? N/A ☒ YES ☐ NO ☐
  If an electronic CTD, all forms and certifications must either be in paper and signed or be electronically signed.

  Additional comments:

- Was the patent information submitted on form FDA 3542a? YES ☒ NO ☐

- Was exclusivity requested? YES, _____ Years NO ☒

NOTE: *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*

- Correctly worded Debarment Certification included with authorized signature? YES ☒ NO ☐
  If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

  NOTE: *Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . . ."*

- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included?
  YES ☐ NO ☒

- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)?
  YES ☐ NO ☒

- Were financial disclosure forms included with authorized signature? YES ☒ NO ☐
  (Forms 3454 and 3455 must be included and must be signed by the APPLICANT, not an agent.)
  NOTE: *Financial disclosure is required for bioequivalence studies that are the basis for approval.*

- Field Copy Certification (that it is a true copy of the CMC technical section)? Y ☒ NO ☐

- Are the PDUFA and Action Goal dates correct in COMIS? YES ☒ NO ☐
  If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Are the trade, established, and applicant names correct in COMIS? YES ☒ NO ☐
  If no, have the Document Room make the corrections.
  Is the established name correct in COMIS IND(s) file(s): YES ☒ NO ☐
  If no, have the Document Room make the corrections.

- List referenced IND numbers: 51,721

- End-of-Phase 2 Meeting(s)? Date(s) _____ NO ☒
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) _____ NO ☒
  If yes, distribute minutes before filing meeting.

Project Management

- Was electronic "Content of Labeling" submitted? YES ☒ NO ☐
  If no, request in 74-day letter.

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?
  YES ☒ NO ☐

- Risk Management Plan consulted to ODS/IO? N/A ☒ YES ☐ NO ☐

- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? Y ☒ NO ☐
- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A ☒ YES ☐ NO ☐
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted?
  N/A ☒ YES ☐ NO ☐

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? N/A ☒ YES ☐ NO ☐
- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES ☐ NO ☐

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?
  YES ☐ NO ☒

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES ☒ NO ☐
  If no, did applicant submit a complete environmental assessment? YES ☐ NO ☐
  If EA submitted, consulted to Florian Zielinski (HFD-357)? YES ☐ NO ☐
- Establishment Evaluation Request (EER) submitted to DMPQ? YES ☒ NO ☐
- If a parenteral product, consulted to Microbiology Team (HFD-805)? YES ☒ NO ☐

ATTACHMENT

MEMO OF FILING MEETING

DATE: November 15, 2005

NDA #: 22-010

DRUG NAMES: Septocaine —

APPLICANT: Deproco

BACKGROUND: Septocaine — is being submitted as a complete response to an approveable action granted to the sponsor via teleconference prior to approval of the original Septocaine in April of 2000. A new NDA has been administratively created for the new dose which contains a half-strength of epinephrine from the already approved dose in NDA 20-971. Fred Hyman is being consulted on the dental portion of the efficacy studies submitted with this application.

(Provide a brief background of the drug, e.g., the molecular entity is already approved and this NDA is for an extended-release formulation; whether another Division is involved; foreign marketing history; etc.)

ATTENDEES: Sharon Hertz, MD; Deputy Director, Dan Mellon, PhD; Pharmacology/Toxicology Supervisor, Yongman Kim, PhD; Statistical Reviewer, Ali Al-Hakim, PhD; Chemistry Reviewer, Suresh Doddapaneni, PhD; Team Leader, Biopharmaceutics, Ravi Harapanhalli, PhD; Branch Chief, Chemistry, Lester Schultheis, MD; Medical Reviewer

ASSIGNED REVIEWERS (including those not present at filing meeting):

Discipline	**Reviewer**
Medical:	Jane Filie, MD
Secondary Medical:	Art Simone, MD
Statistical:	Yongman Kim, PhD
Pharmacology:	Dan Mellon, PhD
Statistical Pharmacology:	
Chemistry:	Mike Adams, PhD
Environmental Assessment (if needed):	
Biopharmaceutical:	Srikanth Nallani, PhD
Microbiology, sterility:	Bryan Riley, PhD
Microbiology, clinical (for antimicrobial products only):	
DSI:	
Regulatory Project Management:	Allison Meyer
Other Consults:	Fred Hyman, MD

Per reviewers, are all parts in English or English translation? YES ☒ NO ☐

If no, explain:

CLINICAL FILE ☒ REFUSE TO FILE ☐

- Clinical site inspection needed? YES ☒ NO ☐

- Advisory Committee Meeting needed? YES, date if known _____ NO ☒

- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? N/A ☒ YES ☐ NO ☐

CLINICAL MICROBIOLOGY	N/A	☒	FILE	☐	REFUSE TO FILE	☐
STATISTICS	N/A	☐	FILE	☒	REFUSE TO FILE	☐
BIOPHARMACEUTICS			FILE	☒	REFUSE TO FILE	☐

- Biopharm. inspection needed? YES ☐ NO ☒

PHARMACOLOGY	N/A	☐	FILE	☒	REFUSE TO FILE	☐

- GLP inspection needed? YES ☐ NO ☒

CHEMISTRY			FILE	☒	REFUSE TO FILE	☐

- Establishment(s) ready for inspection? YES ☒ NO ☐
- Microbiology YES ☒ NO ☐

ELECTRONIC SUBMISSION:
Any comments: not electronic

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

☐ The application is unsuitable for filing. Explain why:

☒ The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.

- ☐ No filing issues have been identified.
- ☒ Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1.☒ Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g, orphan, OTC) are correctly entered into COMIS.

2.☐ If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.

3.☐ If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.

4.☒ If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)

5.☒ Convey document filing issues/no filing issues to applicant by Day 74.

Allison Meyer
Regulatory Project Manager, HFD-170

Appendix A to NDA Regulatory Filing Review

An application is likely to be a 505(b)(2) application if:

(1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
(2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
(4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications

1. Does the application reference a listed drug (approved drug)? YES ☒ NO ☐

   *If "**No**," skip to question 3.*

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s): NDA 20-971 Septocaine

3. The purpose of this and the questions below (questions 3 to 5) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval and that should be referenced as a listed drug in the pending application.

   (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved? YES ☐ NO ☒

   (***Pharmaceutical equivalents*** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and (3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

   *If "**No**," skip to question 4. Otherwise, answer part (b).*

   (b) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES ☐ NO ☐
   (The approved pharmaceutical equivalent(s) should be cited as the listed drug(s).)

   *If "**Yes**," skip to question 6. Otherwise, answer part (c).*

   (c) Have you conferred with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007)? YES ☐ NO ☐

   *If "**No**," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.*

4. (a) Is there a pharmaceutical alternative(s) already approved? YES ☒ NO ☐

   (***Pharmaceutical alternatives*** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

   *If "**No**," skip to question 5. Otherwise, answer part (b).*

   (b) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES ☒ NO ☐
   (The approved pharmaceutical alternative(s) should be cited as the listed drug(s).)

NOTE: *If there is more than one pharmaceutical alternative approved, consult the Director, Division of*

Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007) to determine if the appropriate pharmaceutical alternatives are referenced.

*If "**Yes**," skip to question 6. Otherwise, answer part (c).*

(c) Have you conferred with the Director, Division of Regulatory Policy II, ORP? YES ☐ NO ☐

*If "**No**," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.*

5. (a) Is there an approved drug product that does not meet the definition of "pharmaceutical equivalent" or "pharmaceutical alternative," as provided in questions 3(a) and 4(a), above, but that is otherwise very similar to the proposed product? YES ☐ NO ☐

*If "**No**," skip to question 6.*

*If "**Yes**," please describe how the approved drug product is similar to the proposed one and answer part (b) of this question. Please also contact the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007), to further discuss.*

(b) Is the approved drug product cited as the listed drug? YES ☐ NO ☐

6. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution"). Note: Administrative Split Change in dose, 1/2 strength of epinephrine

7. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)). YES ☐ NO ☒

8. Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 21 CFR 314.101(d)(9)). YES ☐ NO ☒

9. Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application should be refused for filing under 21 CFR 314.101(d)(9). YES ☐ NO ☒

10. Are there certifications for each of the patents listed for the listed drug(s)? YES ☒ NO ☐

11. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
Patent number(s):

NOTE: *IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must* ***subsequently*** *submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)].*

☒ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)
Patent number(s):

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):

☐ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):

12. Did the applicant:

- Identify which parts of the application rely on information (e.g. literature, prior approval of another sponsor's application) that the applicant does not own or to which the applicant does not have a right of reference? YES ☒ NO ☐
- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity? YES ☐ NO ☒
- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug? N/A ☒ YES ☐ NO ☐
- Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).? N/A ☒ YES ☐ NO ☐

13. If the (b)(2) applicant is requesting 3-year exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

- Certification that at least one of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a). YES ☐ NO ☐

- A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval. YES ☐ NO ☐

- EITHER

  The number of the applicant's IND under which the studies essential to approval were conducted.

  IND# _____ NO ☐

  OR

  A certification that the NDA sponsor provided substantial support for the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted? YES ☐ NO ☐

14. Has the Associate Director for Regulatory Affairs, OND, been notified of the existence of the (b)(2) application? YES ☒ NO ☐

Appears This Way
On Original

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: August 31, 2005
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Deproco, Inc.	1/23/06
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE** *(FAX)* **Number** *(Include Area Code)*
(800) 872-8305	(302) 328-5653
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* **IF APPLICABLE**
245-C Quigley Blvd. New Castle, DE 19720	Wayne H. Matelski, Esquire Phone: (202) 857-6340 Arent Fox PLLC Fax: (202) 857-6395 1050 Connecticut Avenue, NW Washington, DC 20036-5339

PRODUCT DESCRIPTION

RECEIVED
JAN 26 2006
CDER CDR

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* 22-010

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
See Attachment	Septocaine®

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
	N/A

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Solution for injection	See Attachment	Nerve block or infiltration

(PROPOSED) INDICATION(S) FOR USE:
For infiltration or nerve block anesthesia for dentistry

APPLICATION DESCRIPTION

APPLICATION TYPE *(check one)* ☒ NEW DRUG APPLICATION (CDA, 21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b)(1) ☒ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug _____ Holder of Approved Application _____

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☐ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☒ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION
Financial Disclosures for Clinical Investigators

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

See Attachment

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

NDA 20-971

This application contains the following items: *(Check all that apply)*	
☐	1. Index
☐	2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50 (c))
☐	4. Chemistry section
☐	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☐	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
☐	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
☐	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
☐	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
☐	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
☐	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
☐	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
☐	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
☐	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
☐	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
☐	15. Establishment description (21 CFR Part 600, if applicable)
☐	16. Debarment certification (FD&C Act 306 (k)(1))
☒	17. Field copy certification (21 CFR 314.50 (l)(3))
☐	18. User Fee Cover Sheet (Form FDA 3397)
☒	19. Financial Information (21 CFR Part 54)
☐	20. OTHER *(Specify)*

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.
The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.
Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
Wayne H. Matelski /BW	Wayne H. Matelski, Esquire Counsel and U.S. Agent	1/23/06

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
Arent Fox PLLC, 1050 Connecticut Avenue, NW, Washington, DC 20036-5339	(202) 857-6340

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CDER, HFD-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER (HFD-94)
12229 Wilkins Avenue
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

ATTACHMENT TO FDA FORM 356h – NDA 22-010

Established Name (e.g., Proper name, USP/USAN name):

Articaine Hydrochloride 4% with Epinephrine 1:200,000 Injection

Strength:

Articaine Hydrochloride 4% with Epinephrine 1:200,000

Establishment Information:

Septocaine® — is manufactured by:

Novocol Pharmaceutical of Canada, Inc.
25 Wolseley Court
Cambridge, Ontario N1R 6X3
Canada

The manufacturers of articaine hydrochloride are:

[ ]

[ ]

The manufacturer of epinephrine is:

[ ]

The manufacturers of the cartridges are:

[ ]

[ ]

[ ]

[ ]

The manufacturers of the cap and seal cover are:

[ ]

[ ]

The manufacturer of the plunger is:

[ ]

[ ]

The manufacturer of the _____ s:

[ ]

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-971
NDA 22-010

Arent Fox PLLC
1050 Connecticut Avenue, NW
Washington, DC 20036-5339

Attention: Wayne Matelski
Counsel to and US Agent for Deproco, Inc

Dear Mr. Matelski:

Reference is made to your approved NDA 20-971, Septocaine® (articaine HCl 4% and epinephrine 1:100,000 injection).

We also refer to your September 29, 2005 supplement, received September 30, 2005, for Septocaine® (articaine HCl 4% and epinephrine 1:200,000 injection). Because this supplement is a resubmission of a product strength submitted in your original submission of NDA 20-971, rather than a new product strength, for administrative reasons, we have split this application and assigned NDA 22-010 to the 1:200,000 strength product. The original receipt date for NDA 22-010 is considered to be the same as that of NDA 20-971, that is March 30, 1998. We consider your September 29, 2005, submission a complete, Class 2 response to previously submitted NDA 20-971 (new assigned NDA 22-010). Therefore, the user fee goal date is March 30, 2006.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirement. We are deferring submission of your pediatric studies until December 31, 2008. However, in the interim, please submit your pediatric drug development plans within 120 days from the date of this letter unless you believe a waiver is appropriate.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of section 2 of the Pediatric Research Equity Act (PREA) within 60 days from the date of this letter. We will notify you within 120 days of receipt of your response whether a waiver is granted. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric

exclusivity). You should refer to the Guidance for Industry on Qualifying for Pediatric Exclusivity (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" in addition to your plans for pediatric drug development described above. Please note that satisfaction of the requirements in section 2 of PREA alone may not qualify you for pediatric exclusivity.

If you have any question, call me, at (301) 796-1258.

Sincerely,

[See appended electronic signature page]

Allison Meyer
Regulatory Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Allison Meyer
11/23/2005 10:39:22 AM

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Arent Fox
ATTORNEYS AT LAW

Wayne H. Matelski
202.857.6340 DIRECT
202.857.6395 FAX
matelski.wayne@arentfox.com

September 29, 2005

VIA FEDERAL EXPRESS

Document Control Room
Division of Anesthesia, Analgesia, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5901-B Ammendale Road (HFD-143)
Beltsville, MD 20705

Re: Supplement to NDA 20-971
Septocaine® (Articaine Hydrochloride 4% (40 mg/mL) with Epinephrine 1:100,000 or 1:200,000 Injection)
Sponsor: Deproco, Inc.

Prior Approval Supplement

Dear Sir or Madam:

On behalf of Deproco, Inc., the Sponsor of NDA 20-971, and its affiliated manufacturing company, Novocol Pharmaceutical of Canada, Inc., I am herewith submitting a supplemental application requesting approval of a second formulation of Articaine Hydrochloride 4% with Epinephrine under the trade name "Septocaine® —" (Articaine Hydrochloride 4% with Epinephrine 1:200,000 Injection). In addition, coincident with this request, Deproco is seeking approval to change the trade name for the currently approved formulation of Articaine Hydrochloride 4% with Epinephrine 1:100,000 Injection from "Septocaine®" to "Septocaine® —," in order to adequately distinguish between the two formulations and prevent confusion. Thus, under the Sponsor's proposal, the two formulations would be marketed under the trade names Septocaine® — and Septocaine® —

BACKGROUND

By way of background, as you may recall, Septocaine® — was included in the original application for NDA 20-971. Indeed, during the pre-IND meeting with the Reviewing Division on May 10, 1996 and a subsequent meeting on January 10, 1997, after explaining its proposed drug development plan to the Agency, Deproco and Agency representatives agreed that the NDA could cover both Articaine Hydrochloride 4% with Epinephrine 1:100,000[1/] and Articaine

[1] In the original NDA, this formulation was referred to as "Septanest® —."

3

Hydrochloride 4% with Epinephrine 1:200,000[2]. During the January 1997 meeting, the Agency agreed that the proposed development plan (which, in addition to Phase 3 studies on Septocaine® —, included, at the Agency's request, a pharmacokinetic/efficacy study using Septocaine® —) would be adequate to approve both products. The Agency further agreed that it was not necessary to independently test Septocaine® — for safety. In reliance upon the Agency's guidance, Deproco implemented the agreed-upon drug development plan and, on March 30, 1998, submitted NDA 20-971 covering both formulations. In accordance with the Prescription Drug User Fee Act of 1992, the Sponsor paid the required application fee associated with this NDA upon submission of the application. The NDA was received by FDA on March 30, 1998, and accepted for filing by the Agency on May 29, 1998.

In January 1999 and May 1999, the FDA issued to Deproco Approvable Letters, neither of which gave any indication that the Agency would not approve both products. Then, 2½ weeks before the Agency's review goal date for Deproco's response to the second Approvable Letter (and 23 months after submission of the NDA), on a conference call, the Agency raised for the first time the possibility that it would approve Septocaine® —, but would not be able to approve Septocaine® — without additional data. Rather than delay approval of Septocaine® —, Deproco agreed to accept approval of Septocaine® — with the intention of resolving at a later date the Agency's desire for additional data on Septocaine® —. Ultimately, on April 3, 2000, FDA approved Septocaine® — (under the trade name "Septocaine®"), while the second formulation that was the subject of the NDA, Septocaine® —, was not approved.

During 2002 and 2003, Deproco participated in a meeting and on two conference calls with representatives of the Review Division to determine what additional information would be required by the Agency to secure approval of Septocaine® —. To satisfy the Agency's requests, Deproco agreed to conduct four (4) additional Phase 3 clinical trials. These studies have now been completed and data from the studies are included in this supplemental application.

The four (4) additional Phase 3 clinical trials (conducted under IND 51,721) compared Septocaine® — to Septocaine® —. As described in detail in this supplement:

1. The results of the first two studies indicate that the anesthetic characteristics (success rate, onset, and duration) of the two formulations are similar, but are different when compared to the anesthetic characteristics of Articaine Hydrochloride 4% without Epinephrine;

2. The results of the third study indicate that during dental surgery, Septocaine® — provides better visualization of the surgical field and less blood loss than Septocaine® —; and

[2] In the original NDA, this formulation was referred to as "Septanest® —."

3. The results of the fourth study indicate that, at maximum clinical doses: (i) the pharmacokinetics of Septocaine® — are similar to those of Septocaine® —, and (ii) Septocaine® — provides significantly less cardiovascular stimulation than Septocaine® —.

The Sponsor believes that it has satisfied the FDA's request for additional information on Septocaine® — and that these data demonstrate that the formulation is safe and effective under the intended conditions of use.

USER FEE

The Sponsor respectfully submits that this supplemental application is exempt from the requirement for an application fee under the Prescription Drug User Fee Act. That act provides an exemption from the application fee requirement for an NDA or supplemental NDA if an NDA "for the same product" was previously submitted by "the same person," who paid the user fee associated with that application or supplement, and the previous application or supplement "was accepted for filing[] and was not approved or was withdrawn." FDCA § 736(a)(1)(C). In the present case, as noted above, in March 1998, Deproco submitted an NDA for Septocaine® — and Septocaine® — and paid the application fee associated with the NDA. FDA accepted the application for filing on May 29, 1998, but the application, as it related to Septocaine® —, was not approved. Thus, this supplemental application meets the exemption requirements because Deproco previously submitted an NDA for the same product that is the subject of this supplemental NDA, Deproco paid the application fee associated with that NDA, and FDA accepted that application for filing, but the Agency did not approve the NDA with respect to this product. The Center's Office of Regulatory Policy has agreed with the Sponsor's conclusion that a new application fee is not required.[3]

* * * * *

In accordance with the requirements of the Generic Drug Enforcement Act of 1992, and in connection with the supplemental application, to the best of its knowledge, Deproco, Inc. and Novocol Pharmaceutical of Canada, Inc. did not utilize, in any capacity, the services of any person debarred under Section 306 of the Federal Food, Drug and Cosmetic Act.

Need revised debarment certification

Pursuant to the provisions of 21 C.F.R. § 314.50(l)(3), I hereby certify that I am sending to the FDA's Philadelphia District Office a true copy of this Supplemental Application.

[3] Conversation with Ms. Beverly Friedman (Office of Regulatory Policy) on August 29, 2005, following consideration of Sponsor's letter of August 19, 2005, to the Office of Regulatory Policy, with a copy to the Review Division.

Should you have any questions, or if we can provide any additional information, please do not hesitate to contact me.

Sincerely,

Wayne H. Matelski
Counsel to and U.S. Agent for Deproco, Inc.
and Novocol Pharmaceutical of Canada, Inc.

Attachments

cc: Thomas Gardine (FDA/Philadelphia District Office)

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On Original

Arent Fox
ATTORNEYS AT LAW

October 17, 2005

Brian P. Waldman
202.857.8971 DIRECT
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waldman.brian@arentfox.com

VIA FEDERAL EXPRESS

Allison Meyer
Food and Drug Administration
10903 New Hampshire Ave,
Building 22, Room 3135
Silver Spring, MD 20993-0002

Re: NDA No. 20-971
Septocaine® (Articaine Hydrochloride 4% (40 mg/mL) with Epinephrine 1:100,000 or 1:200,000 Injection)
Sponsor: Deproco, Inc.
Copies of Correspondence Regarding Septocaine® —

Dear Allison:

As you requested in a telephone conversation earlier today, enclosed please find copies of the following correspondence between Deproco, Inc. and the FDA regarding Septocaine® —.

1. First Approvable Letter from the FDA, January 29, 1999.
2. Second Approvable Letter from the FDA, May 7, 1999.
3. Letter from FDA notifying Deproco, Inc. that the February 3, 2000 resubmission was a complete class 1 response to the May 7, 1999 action letter.
4. Letter from FDA providing a copy of the minutes from the March 16, 2000 teleconference between FDA and Deproco, Inc.
5. Deproco, Inc. Response to FDA Questions, March 22, 2000.
6. "Septocaine® —" Approval Letter, April 3, 2000.

Please contact us if you have any questions.

Sincerely,

Brian P. Waldman 1808

Brian P. Waldman
Counsel to Deproco, Inc.

Enclosures

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NDA 20-971

Deproco, Inc.
c/o Arent Fox Kintner Plotkin & Kahn, PLLC
1050 Connecticut Avenue, N.W.
Washington, DC 20036-5339

APR 0 3 2000

Attention: Wayne Matelski, Esq.

Dear Mr. Matelski:

Please refer to the new drug application (NDA) dated March 30, 1998, received March 30, 1998, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Septocaine™ (articaine hydrochloride 4% with epinephrine 1:100,000 for injection).

We also refer to your amendments dated April 29, May 18 and 26, August 21, September 10, October 23, and December 1, 1998, March 9 and May 4, 1999, and February 3, 24, and 28 and March 16, 2000. Your submission of February 3, 2000, constituted a complete response to our May 7, 1999, action letter.

This new drug application provides for the use of Septocaine™ for local, infiltrative, or conductive anesthesia in both simple and complex dental and periodontal procedures.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon enclosed labeling text. As agreed, the established name will be printed below the trade name within the same background for the immediate container and carton labels at the next printing. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert) and the immediate container and carton labels submitted March 31, 2000, with the change listed above. Marketing the product with FPL that is not identical to the approved labeling may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 20-971." Approval of this submission by FDA is not required before the labeling is used.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We note that you have fulfilled the pediatric study requirement at this time for children aged 4 or older. We are waiving the pediatric study requirement for children less than 4 years old for this action on this application.

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Laura Governale, Pharm.D., Regulatory Project Manager, at (301) 827-7410.

Sincerely,

Lisa D. Rarick, M.D.
Deputy Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

Septocaine™

(articaine hydrochloride 4% (40 mg/mL) with epinephrine 1:100,000 injection)

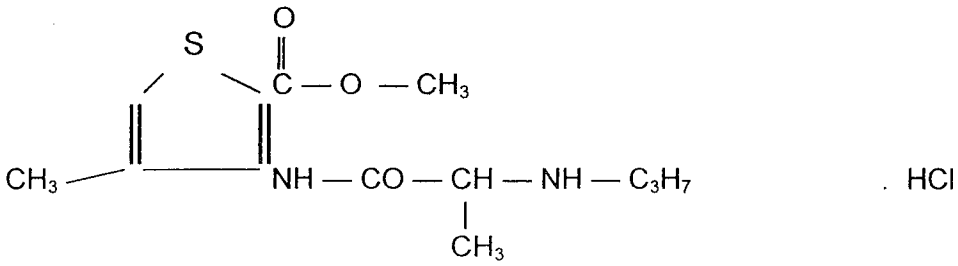
APR 0 3 2000

For Infiltration and Nerve Block Anesthesia

APPROVED

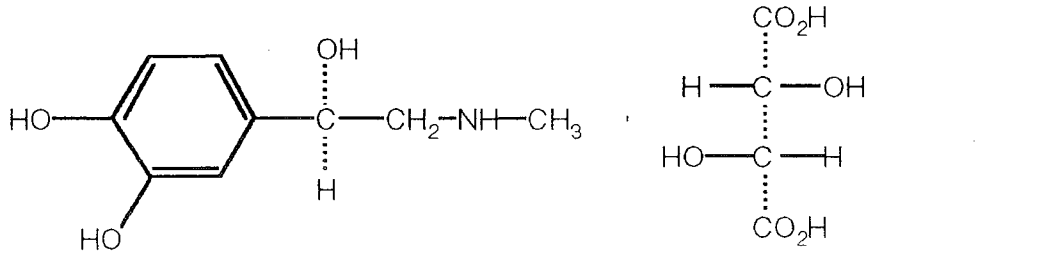
DESCRIPTION

Septocaine™ injection is a sterile, aqueous solution that contains articaine HCl 4% (40 mg/mL) with epinephrine bitartrate in a 1:100,000 strength. Articaine HCl is a local anesthetic, which is chemically designated as 4-methyl-3-[2-(propylamino)-propionamido]-2-thiophene-carboxylic acid, methyl ester hydrochloride and is a racemic mixture. Articaine HCl has a molecular weight of 320.84 and the molecular and structural formulae are displayed below :



$C_{13}H_{20}N_2O_3S$, HCl

Articaine HCl has a partition coefficient in n-octanol/ Soerensen buffer (pH : 7.35) of 17 and a pKa of 7.8. Epinephrine bitartrate, (-)-1-(3,4-Dihydroxyphenyl)-2-methylamino-ethanol (+) tartrate (1:1) salt, is a vasoconstrictor that is added to articaine HCl in a concentration of 1:100,000 as the free base. It has a molecular weight of 333.3. The molecular and structural formulae are displayed below:



$C_9H_{13}NO_3$. $C_4H_6O_6$

Septocaine™ contains articaine HCl (40mg/mL), epinephrine as bitartrate (1:100,000), sodium chloride (1.6 mg/mL), and sodium metabisulfite (0.5 mg/mL). The product is formulated with a 15% overage of epinephrine. The pH is adjusted to 5.0 with sodium hydroxide.

CLINICAL PHARMACOLOGY

Pharmacokinetics

Absorption : Following dental injection by the submucosal route of an articaine solution containing 1:200,000 epinephrine, articaine reaches peak blood concentration about 25 minutes after a single dose injection and 48 minutes after three doses. Peak plasma levels of articaine achieved after 68 and 204 mg doses are 385 and 900 ng/mL, respectively.

Distribution : Approximately 60 to 9[illegible]% of articaine HCl [illegible]und t[illegible]an se[illegible] albumin and γ-globulins at 37°C in vitro.

Metabolism : Articaine HCl is rapidly metabolized by plasma carboxyesterase to its primary metabolite, articainic acid, which is inactive. In vitro studies show that the human liver microsomal P450 isoenzyme system metabolizes approximately 5% to 10% of available articaine with nearly quantitative conversion to articainic acid.

Excretion : The elimination half-life of articaine is about 1.8 hours and that of articainic acid is about 1.5 hours. Articaine is excreted primarily through urine with 53 - 57% of the administered dose eliminated in the first 24 hours following submucosal administration. Articainic acid is the primary metabolite in urine. A minor metabolite, articainic acid glucuronide, is also excreted in urine. Articaine constitutes only 2% of the total dose excreted in urine.

Special populations

Effect of Age : No studies have been performed to evaluate the pharmacokinetics of Septocaine™ injection in geriatric or pediatric subjects.

Race : There is insufficient information to determine whether the pharmacokinetics of Septocaine™ injection differs by race.

Renal and Hepatic Insufficiency : No studies have been performed with Septocaine™ injection in patients with renal or hepatic dysfunction.

Pharmacodynamics

Mechanism of action : Articaine HCl is a member of the amino amide class of local anesthetics. Local anesthetics block the generation and conduction of nerve impulses, presumably by increasing the threshold for electrical excitation in the nerve, by slowing the propagation of the nerve impulse, and by reducing the rate of rise of the action potential. In general, the progression of anesthesia is related to the diameter, myelination and conduction velocity of the affected nerve fibers. Clinically, the order of loss of nerve function is as follows: (1) pain, (2) temperature, (3) touch, (4) proprioception, and (5) skeletal muscle tone. Epinephrine is a vasoconstrictor added to articaine HCl to slow absorption into the general circulation and thus prolong maintenance of an active tissue concentration.

The onset of anesthesia following administration of Septocaine™ has been shown to be within 1 to 6 minutes of injection. Complete anesthesia lasts approximately 1 hour.

Administration of articaine HCl with epinephrine results in a 3- to 5-fold increase in plasma epinephrine concentrations compared to baseline; however, in healthy adults it does not appear to be associated with marked increases in blood pressure or heart rate, except in the case of accidental intravascular injection (See WARNINGS).

CLINICAL TRIALS

Three randomized, double-blind, active-controlled studies were designed to evaluate effectiveness of Septocaine™ as a dental anesthetic. A total of 882 patients received Septocaine™. Of these, 7% were between 4 and 16 years old, 87% were between 17 and 65 years old, and 6% were at least 65 years old. In addition, 53% of patients were female and 47% were male, with a racial/ethnic distribution of 73% white, 11% Hispanic, 8% black, 5% Asian, and 3% "other" races/ethnicities. These patients underwent simple dental procedures such as single uncomplicated extractions, routine operative procedures, single apical resections, and single crown procedures, and complex dental procedures such as multiple extractions, multiple crowns and/or bridge procedures, multiple apical resections, alveolectomies, muco-gingival operations, and other surgical procedures on the bone. Septocaine™ was administered as

submucosal infiltration and immediately following the procedure by having the patient and investigator rate the patient's procedural pain using a 10 cm visual analog scale (VAS), in which a score of zero represented no pain, and a score of 10 represented the worst pain imaginable.

Mean patient and investigator VAS pain scores were 0.3 - 0.4 cm for simple procedures and 0.5 - 0.6 cm for complex procedures. These values are summarized in Table 1.

Table 1. Summary of VAS Pain Scores

	SEPTOCAINE™ (articaine HCl 4% with epinephrine 1:100,000)	
	Simple Procedures	Complex Procedures
Number of patients	674	207
Investigator score (cm)		
Mean	0.3	0.5
Median	0.0	0.2
Range	0 - 9.0	0 - 7.3
Patient score (cm)		
Mean	0.4	0.6
Median	0.0	0.2
Range	0 - 8.0	0 - 8.7

INDICATIONS AND USAGE

Septocaine™ is indicated for local, infiltrative, or conductive anesthesia in both simple and complex dental and periodontal procedures.

CONTRAINDICATIONS

Septocaine™ is contraindicated in patients with a known history of hypersensitivity to local anesthetics of the amide type, or in patients with known hypersensitivity to sodium metabisulfite.

WARNINGS

ACCIDENTAL INTRAVASCULAR INJECTION MAY BE ASSOCIATED WITH CONVULSIONS, FOLLOWED BY CENTRAL NERVOUS SYSTEM OR CARDIORESPIRATORY DEPRESSION AND COMA, PROGRESSING ULTIMATELY TO RESPIRATORY ARREST. DENTAL PRACTITIONERS AND/OR CLINICIANS WHO EMPLOY LOCAL ANESTHETIC AGENTS SHOULD BE WELL VERSED IN DIAGNOSIS AND MANAGEMENT OF EMERGENCIES THAT MAY ARISE FROM THEIR USE. RESUSCITATIVE EQUIPMENT, OXYGEN, AND OTHER RESUSCITATIVE DRUGS SHOULD BE AVAILABLE FOR IMMEDIATE USE.

Intravascular injections should be avoided. To avoid intravascular injection, aspiration should be performed before Septocaine™ is injected. The needle must be repositioned until no return of blood can be elicited by aspiration. Note, however, that the absence of blood in the syringe does not guarantee that intravascular injection has been avoided.

Septocaine™ contains epinephrine that can cause local tissue necrosis or systemic toxicity. Usual precautions for epinephrine administration should be observed.

Septocaine™ contains sodium metabisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown. Sulfite sensitivity is seen more frequently in asthmatic than in non-asthmatic people.

PRECAUTIONS

General : Resuscitative equipment, oxygen, and other resuscitative drugs should be available for immediate use (See WARNINGS). The lowest dosage that results in effective anesthesia should be used to avoid high plasma levels and serious adverse effects. Repeated doses of Septocaine™ may cause significant increases in blood levels with each repeated dose because of possible accumulation of the drug or its metabolites. Tolerance to elevated blood levels varies with the status of the patient. Debilitated patients, elderly patients, acutely ill patients and pediatric patients should be given reduced doses commensurate with their age and physical condition. Septocaine™ should also be used with caution in patients with heart block.

Local anesthetic solutions, such as Septocaine™, containing a vasoconstrictor should be used cautiously. Patients with peripheral vascular disease and those with hypertensive vascular disease may exhibit exaggerated vasoconstrictor response. Ischemic injury or necrosis may result. Septocaine™ should be used with caution in patients during or following the administration of potent general anesthetic agents, since cardiac arrhythmias may occur under such conditions.

Systemic absorption of local anesthetics can produce effects on the central nervous and cardiovascular systems. At blood concentrations achieved with therapeutic doses, changes in cardiac conduction, excitability, refractoriness, contractility, and peripheral vascular resistance are minimal. However, toxic blood concentrations depress cardiac conduction and excitability, which may lead to atrioventricular block, ventricular arrhythmias, and cardiac arrest, sometimes resulting in fatalities. In addition, myocardial contractility is depressed and peripheral vasodilation occurs, leading to decreased cardiac output and arterial blood pressure.

Careful and constant monitoring of cardiovascular and respiratory (adequacy of ventilation) vital signs and the patient's state of consciousness should be accomplished after each local anesthetic injection. It should be kept in mind at such times that restlessness, anxiety, tinnitus, dizziness, blurred vision, tremors, depression, or drowsiness may be early warning signs of central nervous system toxicity.

In vitro studies show that about 5% to 10% of articaine is metabolized by the human liver microsomal P450 isoenzyme system. However, because no studies have been performed in patients with liver dysfunction, caution should be used in patients with severe hepatic disease. Septocaine™ should also be used with caution in patients with impaired cardiovascular function since they may be less able to compensate for functional changes associated with the prolongation of A-V conduction produced by these drugs.

Small doses of local anesthetics injected in dental blocks may produce adverse reactions similar to systemic toxicity seen with unintentional intravascular injections of larger doses. Confusion, convulsions, respiratory depression and/or respiratory arrest, and cardiovascular stimulation or depression have been reported. These reactions may be due to intra-arterial injection of the local anesthetic with retrograde flow to the cerebral circulation. Patients receiving these blocks should be observed constantly. Resuscitative equipment and personnel for treating adverse reactions should be immediately available. Dosage recommendations should not be exceeded. (See DOSAGE and ADMINISTRATION)

Information for Patients : The patient should be informed in advance of the possibility of temporary loss of sensation and muscle function following infiltration and nerve block injections.

Clinically Significant Drug Interactions : The administration of local anesthetic solutions containing epinephrine to patients receiving monoamine oxidase inhibitors or tricyclic antidepressants may produce severe, prolonged hypertension. Phenothiazines and butyrophenones may reduce or reverse the

pressor effect of epinephrine. Concurrent use of these should generally be avoided. In situations when concurrent therapy is necessary, careful patient monitoring is essential.

Carcinogenesis, Mutagenesis, Impairment of Fertility : Studies to evaluate the carcinogenic potential of articaine HCl in animals have not been conducted. Five standard mutagenicity tests, including three in vitro tests (the nonmammalian Ames test, the mammalian Chinese hamster ovary chromosomal aberration test and a mammalian gene mutation test with articaine HCl) and two in vivo mouse micronucleous tests (one with Septocaine™ and one with articaine HCl alone) showed no mutagenic effects. No effects on male or female fertility were observed in rats for Septocaine™ administered subcutaneously in doses up to 80 mg/kg/day (approximately two times the maximum male and female recommended human dose on a mg/m^2 basis).

Pregnancy : Teratogenic Effects-Pregnancy Category C.

In developmental studies, no embryofetal toxicities were observed when Trade Narne® was administered subcutaneously throughout organogenesis at doses up to 40 mg/kg in rabbits and 80 mg/kg in rats (approximately 2 times the maximum recommended human dose on a mg/m^2 basis). In rabbits, 80 mg/kg (approximately 4 times the maximum recommended human dose on a mg/m^2 basis) did cause fetal death and increase fetal skeletal variations, but these effects may be attributable to the severe matemal toxicity, including seizures, observed at this dose.

When articaine hydrochloride was administered subcutaneously to rats throughout gestation and lactation, 80 mg/kg (approximately 2 times the maximum recommended human dose on a mg/m^2 basis) increased the number of stillbirths and adversely affected passive avoidance, a measure of learning, in pups. This dose also produced severe matemal toxicity in some animals. A dose of 40 mg/kg (approximately equal to the maximum recommended human dose on a mg/m^2 basis) did not produce these effects. A similar study using Septocaine™ (articaine hydrochloride and epinephrine 1:100,000) rather than articaine hydrochloride alone produce maternal toxicity, but no effects of offspring.

There are no adequate and well-controlled studies in pregnant women. Animal reproduction studies are not always predictive of human response. Septocaine™ should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers : It is not known whether articaine is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Septocaine™ is administered to a nursing woman.

Pediatric Use : In clinical trials, 61 pediatric patients between the ages of 4 and 16 years received Septocaine™. Among these pediatric patients, doses from 0.76 mg/kg to 5.65 mg/kg (0.9 to 5.1 mL) were administered safely to 51 patients for simple procedures and doses between 0.37 mg/kg and 7.48 mg/kg (0.7 to 3.9 mL) were administered safely to 10 patients for complex procedures. However, there was insufficient exposure to Septocaine™ at doses greater than 7.00 mg/kg in order to assess its safety in pediatric patients. No unusual adverse events were noted in these patients. Approximately 13% of these pediatric patients required additional injections of anesthetic for complete anesthesia. Safety and effectiveness in pediatric patients below the age of 4 years have not been established. Dosages in pediatric patients should be reduced, commensurate with age, body weight, and physical condition. See DOSAGE AND ADMINISTRATION.

Geriatric Use : In clinical trials, 54 patients between the ages of 65 and 75 years, and 11 patients 75 years and over received Septocaine™. Among all patients between 65 and 75 years, doses from 0.43 mg/kg to 4.76 mg/kg (0.9 to 11.9 mL) were administered safely to 35 patients for simple procedures and doses from 1.05 mg/kg to 4.27 mg/kg (1.3 to 6.8 mL) were administered safely to 19 patients for complex procedures. Among the 11 patients ≥ 75 years old, doses from 0.78 mg/kg to 4.76 mg/kg (1.3 to 11.9 mL) were administered safely to 7 patients for simple procedures and doses of 1.12 mg/kg to 2.17 mg/kg (1.3 to 5.1 mL) were administered to 4 patients for complex procedures. No overall differences in safety or effectiveness were observed between elderly subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Approximately 6% of patients

between the ages of 65 and 75 years and one of the 11 patients 75 years of age or older required additional injections of anesthetic for complete anesthesia compared with 11% of patients between 17 and 65 years old who required additional injections.

ADVERSE REACTIONS

Reactions to Septocaine™ are characteristic of those associated with other amide-type local anesthetics. Adverse reactions to this group of drugs may also result from excessive plasma levels, which may be due to overdosage, unintentional intravascular injection, or slow metabolic degradation.

The reported adverse events are derived from clinical trials in the US and UK. Of the 1325 patients treated in the primary clinical trials, 882 were exposed to Septocaine™.

Table 2
Adverse Events in controlled trials with an incidence of 1% or greater in patients administered Septocaine™ (articaine hydrochloride 4% (40 mg/mL) with epinephrine 1:100,000 Injection)

Body system	Septocaine™ N (%)
Number of Patients	882 (100%)
Body As A Whole	
Face Edema	13 (1%)
Headache	31 (4%)
Infection	10 (1%)
Pain	114 (13%)
Digestive System	
Gingivitis	13 (1%)
Nervous system	
Paresthesia	11 (1%)

The following list includes adverse and intercurrent events that were recorded in 1 or more patients, but occurred at an overall rate of less than one percent, and were considered clinically relevant .

Body as a Whole - abdominal pain, accidental injury, asthenia, back pain, injection site pain, malaise, neck pain.

Cardiovascular System - hemorrhage, migraine, syncope, tachycardia.

Digestive System - constipation, diarrhea, dyspepsia, glossitis, gum hemorrhage, mouth ulceration, nausea, stomatitis, tongue edemas, tooth disorder, vomiting.

Hemic and Lymphatic System - ecchymosis, lymphadenopathy.

Metabolic and Nutritional System - edema, thirst.

Musculoskeletal System - arthralgia, myalgia, osteomyelitis.

Nervous System - dizziness, dry mouth, facial paralysis, hyperesthesia, increased salivation, nervousness, neuropathy, paresthesia, somnolence.

Respiratory System - pharyngitis, rhinitis.

Skin and Appendages - pruritis, skin disorder.

Special Senses - ear pain, taste perversion

Urogenital System - dysmenorrhea.

OVERDOSAGE

Acute emergencies from local anesthetics are generally related to high plasma levels encountered during therapeutic use of local anesthetics or to unintended subarachnoid injection of local anesthetic solution (see **WARNINGS, PRECAUTIONS, General,** and **ADVERSE REACTIONS**).

Management of Local Anesthetic Emergencies : The first consideration is prevention, best accomplished by careful and constant monitoring of cardiovascular and respiratory vital signs and the patient's state of consciousness after each local anesthetic injection. At the first sign of change, oxygen should be administered.

The first step in the management of convulsions, as well as hypoventilation, consists of immediate attention to the maintenance of a patent airway and assisted or controlled ventilation as needed. The adequacy of the circulation should be assessed. Should convulsions persist despite adequate respiratory support, treatment with appropriate anticonvulsant therapy is indicated. The practitioner should be familiar, prior to the use of local anesthetics, with the use of anticonvulsant drugs. Supportive treatment of circulatory depression may require administration of intravenous fluids and, when appropriate, a vasopressor.

If not treated immediately, both convulsions and cardiovascular depression can result in hypoxia, acidosis, bradycardia, arrhythmias, and cardiac arrest. If cardiac arrest should occur, standard cardiopulmonary resuscitative measures should be instituted.

DOSAGE AND ADMINISTRATION

Table 3 (Recommended Dosages) summarizes the recommended volumes and concentrations of Septocaine™ for various types of anesthetic procedures. The dosages suggested in this table are for normal healthy adults, administered by submucosal infiltration and/or nerve block.

Table 3.Recommended Dosages

PROCEDURE	Septocaine™ Injection	
	Vol (mL)	Total Dose of Articaine HCl (mg)
Infiltration	0.5-2.5	20-100
Nerve Block	0.5-3.4	20-136
Oral Surgery	1.0-5.1	40-204
THE ABOVE SUGGESTED VOLUMES SERVE ONLY AS A GUIDE. OTHER VOLUMES MAY BE USED PROVIDED THE TOTAL MAXIMUM RECOMMENDED DOSE IS NOT EXCEEDED.		

These recommended doses serve only as a guide to the amount of anesthetic required for most routine procedures. The actual volumes to be used depend on a number of factors such as type and extent of surgical procedure, depth of anesthesia, degree of muscular relaxation, and condition of the patient. In all cases, the smallest dose that will produce the desired result should be given. Dosages should be reduced for pediatric patients, elderly patients, and patients with cardiac and/or liver disease. (See **PRECAUTIONS, Pediatric Use** and **Geriatric Use**).

The onset of anesthesia, and the duration of anesthesia are proportional to the volume and concentration (i.e., total dose) of local anesthetic used. Caution should be exercised when employing large volumes since the incidence of side effects may be dose-related.

MAXIMUM RECOMMENDED DOSAGES

Adults : For normal healthy adults, the maximum dose of articaine HCl administered by submucosal infiltration and/or nerve block should not exceed 7 mg/kg (0.175 mL/kg) or 3.2 mg/lb (0.0795 mL/lb) of body weight.

Pediatric Patients : Use in pediatric patients under 4 years of age is not recommended. 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 7 mg/kg (0.175 mL/kg) or 3.2 mg/lb (0.0795 mL/lb) of body weight.

STERILIZATION, STORAGE, AND TECHNICAL PROCEDURES

For chemical disinfection of the carpule, either isopropyl alcohol (91%) or ethyl alcohol (70%) is recommended. Many commercially available brands of isopropyl (rubbing) alcohol, as well as solutions of ethyl alcohol not of U.S.P. grade, contain denaturants that are injurious to rubber and therefore are not to be used.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

HOW SUPPLIED

Septocaine™ (articaine HCl 4% with epinephrine 1:100,000 injection) is available in 1.7 mL glass cartridges, in boxes of 50 cartridges. The product is formulated with a 15% overage of epinephrine.

NDC XXXXX-XXX-XX Box of 50 cartridges

Store at 25°C (77°F) with brief excursions permitted between 15° and 30°C (59°F-86°F) (see USP controlled room temperature). Protect from light.

Manufactured in France by : Spécialités SEPTODONT, France.
Distributed by: SEPTODONT, Inc.,
245, Quigley Boulevard-Suite C
New Castle, Delaware 19720

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NDA 20-971

Deproco, Inc.
c/o Arent Fox Kintner Plotkin & Kahn
1050 Connecticut Avenue, N.W.
Washington, DC 20036-5339

MAR 2 0 2000

Attention: Wayne Matelski, Esq.

Dear Mr. Matelski:

Please refer to the meeting between representatives of your firm and FDA on March 16, 2000. The purpose of the meeting was to relay labeling changes to the package insert.

A copy of our minutes of that meeting is enclosed. These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you have regarding the meeting outcomes.

If you have any questions, call me at (301) 827-7410.

Sincerely,

Laura Governale

Laura Governale, Pharm.D.
Regulatory Project Manager
Division of Anesthetic, Critical Care, and
Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

TELECONFERENCE MINUTES

Meeting Date: March 16, 2000 **Time:** 2:00 – 2:30 pm
Location: 9B45 Conference Room
NDA: 20-971
Drug: Septanest® 1:100,000 and Septanest® 1:200,000
Sponsor: Deproco, Inc.
Indication: Infiltration or nerve block anesthesia for dentistry
Type of Meeting: Type C Teleconference
Meeting Chair: Cynthia McCormick, M.D., Director
Minutes Recorder: Laura Governale, Pharm.D., Regulatory Project Manager

MAR 2 0 2000

FDA Attendees:	Titles:	Offices:
Cynthia McCormick, M.D.	Director	HFD-170
Bob Rappaport, M.D.	Deputy Director	HFD-170
Harold Blatt, M.D.	Medical Reviewer	HFD-170
Laura Governale, Pharm. D.	Regulatory Project Manager	HFD-170

Participants:	Titles:
Wayne Matelski, Esq.	
Brain Waldman	

Meeting Objective: The purpose of this teleconference was to relay labeling changes and present additional requests for information to the sponsor regarding this NDA.

General Discussion: Following introductions, Dr. McCormick presented the issues surrounding this NDA to the sponsor. The review team has made some changes to the package insert labeling. In addition, the Agency would like the sponsor to submit a justification for the formulation containing epinephrine concentration 1:200,000. After re-reviewing the studies that were submitted with the original submission, the Agency questions the need for this strength. All the clinical data were based on epinephrine strength 1: 100,000. The sponsor was instructed to submit their case for 1:200,000 strength of epinephrine. The Agency requires more than a theoretical reason to approve this strength; therefore, data from this submission should be referenced in the argument.

In terms of labeling, the Agency is moving away from percentage designation to mg/mL for indicating product strength. Mr. Matelski stated that the change would not be a problem for the package insert; however, there may not be enough room on the cartridge for the mg/mL designation. He will check into this.

Dr. McCormick relayed additional labeling changes to the sponsor. The label has been modified to include a statement of 15% epinephrine overage, and some editorial changes in the PK section. The Clinical Trials section of the label has undergone greater changes. The

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"Septanest" has been replaced with "Trade Name" throughout the label pending resolution of the trade name issue. The remainder of the changes were minor and editorial in nature. The Agency will fax a copy of the revised label to the sponsor.

Mr. Matelski presented a status report on the trade name issue. A preliminary response to the questions raised in the March 8, 2000, teleconference will be submitted to the Agency later today. A complete response is not included because the data are still being compiled. After conversing with representatives in other countries marketing both Citanest® and Septanest®, no confusion reports have been identified thus far. France has not received such reports and neither have UK and Canada. A full response should be expected by next Tuesday, March 21, 2000.

Dr. McCormick inquired whether the sponsor intended not to change the trade name. Mr. Matelski replied that he hopes to justify that Septanest®, the current trade name, is a valid name. Mr. Matelski further added that the current name, Septanest® is used throughout the world and Astra, the marketer of Citanest® has not filed any trademark issues. Furthermore, the sulfite allergy concern may be greater between Citanest® Plain and Citanest® Forte, since the latter formulation contains sulfites. There is a greater potential for confusion within the same drug family name than between Citanest® and Septanest®. In addition, dentists generally use only one dental anesthetic in the office; therefore, the potential for confusion between these two trade names is lessened. Dr. Blatt was not in agreement that this is a routine practice.

Dr. Blatt commented that in his experience, dentists typically use 2-3 different dental anesthetics in practice. Mr. Matelski added this is not the main argument for the trade name issue and that more data will be sent to support the trade name Septanest®. From what has been gathered so far, Septanest® is a safer product than Citanest®.

Dr. McCormick agreed that the occurrence of methemoglobinemia is more an issue with Citanest® than Septanest®. However, reducing the potential name confusion by changing the trade name would be a better assurance of preventing this ADR.

Mr. Matelski closed this issue by offering to submit information in support of the trade name, Septanest®. The submission being put together for today will contain a revised FDA Form 356h as a 505(b)2 application and a response to sulfite warning labels on cartridges and cans. Color copies of the cans and boxes will be submitted at a later date. Furthermore, this submission will include cartridges of other products as an example of the imprinting process that will be used for Septanest®.

Dr. McCormick reiterated that the Agency is requesting foreign ADR data for Citanest® and Septanest® only. In addition, if no justification for epinephrine strength 1:200,000 can be found, the Agency may approve only the one strength, 1:100,000.

Dr. McCormick adjourned the teleconference.

Action Items:

- The Agency will provide the sponsor with a copy of the official meeting minutes.
- The Agency will fax a copy of the labeling changes to the sponsor.
- The sponsor will submit additional data in support of the current trade name, Septanest.
- The sponsor will include in today's submission sample cartridges as an example of the imprinting process, revised Form FDA 356h, and wording for sodium metabisulfite warnings.

Minutes prepared by: Laura Governale, Pharm.D.

Laura Governale 3-20-00

Minutes concurred by Chair: Cynthia McCormick, M.D., Director

Cynthia McCormick MD

Appears This Way
On Original

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NDA 20-971

Deproco, Inc.
c/o Arent Fox Kintner Plotkin & Kahn
1050 Connecticut Avenue, N.W.
Washington, DC 20036-5339

MAR 0 1 2000

Attention: Wayne Matelski, Esq.
U.S. Agent for and Counsel to
Specialites Septodont and Deproco, Inc.

Dear Mr. Matelski:

We acknowledge receipt on February 3, 2000, of your February 3, 2000, resubmission to your new drug application (NDA) for Septanest® (articaine hydrochloride 4% with epinephrine 1:100,000 and 1:200,000) solution for injection.

This resubmission contains additional information submitted in response to our May 7, 1999 action letter.

We consider this a complete class 1 response to our action letter. Therefore, the primary user fee goal date is April 3, 2000, and the secondary user fee goal date is June 3, 2000.

If you have any questions, call Laura Governale, Pharm.D., Regulatory Project Manager, at (301) 827-7410.

Sincerely,

Cathie Schumaker
Acting Chief, Project Management Staff
Division of Anesthetic, Critical Care, and
Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

3/2000 TC told 1/500,000 wouldn't be AP'd

NDA 20-971

5/13/99

Arent Fox
1050 Connecticut Avenue, NW
Washington, D.C. 20036-5339

Attention: Wayne H. Matelski, J.D.
United States Agent for and Counsel to
Deproco, Inc. and Specialites Septodont

Dear Mr. Matelski:

Please refer to your pending March 30, 1998 New Drug Application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Septanest — (articaine hydrochloride 4% with Epinephrine 1/200,000 solution injection) and Septanest— (articaine hydrochloride 4% with Epinephrine 1/100,000 solution injection).

We acknowledge receipt of your submissions dated March 9, 1999 and May 4, 1999.

Your submission of March 9, 1999 constituted a complete response to our January 29, 1999 action letter.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following deficiencies:

1) Recently, the FDA conducted an inspection of your drug product manufacturing facility, Specialites Septodont, located at Saint Maur De Fosses, Paris, France for conformance with current good manufacturing practices (cGMP). The inspection report (5/5/1999) revealed that the performance of the facility is unacceptable at this time. The issues involve deviations from current good manufacturing practices. A satisfactory inspection will be required before this application may be approved.

2) The issue of overage has not been satisfactorily addressed. There is a 15% overage in the product for epinephrine. The —% loss in manufacturing has not been satisfactorily accounted for. Please provide documentation of decomposition products or other evidence of loss. Also, based on the —month stability data for three lots, the product can be granted a —month expiration date, not an —month expiration date (based on a —% overage) as you requested.

3) The product should be labeled with the epinephrine strength as it was formulated. Thus, you should report the epinephrine in ratios of 1.15:100,000 and 1.15:200,000 because the epinephrine amount is currently formulated with a 15% overage.

4) The proprietary name that you have proposed in response to the January 29, 1999, approvable letter continues to be unacceptable. The term "——" implies an original strength that was "weak". If that original strength were to be discontinued, the "——" part of the trademark could be misleading.

   Additionally, the agency has had numerous reports over the years of "——" being confused with the number "forty". Consequently, inappropriate doses or inappropriate numbers of doses of medication have been administered.

In addition, it will be necessary for you to submit revised draft labeling for the drug. The labeling should be identical in content to the enclosed labeling (text for the package insert).

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update your NDA by submitting all safety information you now have regarding your new drug. Please provide updated information as listed below. The update should cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels, etc.

1. Retabulation of all safety data including results of trials that were still ongoing at the time of NDA submission. The tabulation can take the same form as in your initial submission. Tables comparing adverse reactions at the time the NDA was submitted versus now will certainly facilitate review.

2. Retabulation of drop-outs with new drop-outs identified. Discuss, if appropriate.

3. Details of any significant changes or findings.

4. Summary of worldwide experience on the safety of this drug.

5. Case report forms for each patient who died during a clinical study or who did not complete a study because of an adverse event.

6. English translations of any approved foreign labeling not previously submitted.

7. Information suggesting a substantial difference in the rate of occurrence of common, but less serious, adverse events.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not

final print. Please send one copy to the Division of Anesthetic, Critical Care, and Addiction Drug Products, HFD-170 and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal or telephone conference with the Division of Anesthetic, Critical Care, and Addiction Drug Products, HFD-170 to discuss what further steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, contact Susmita Samanta, Regulatory Project Manager, at 301-827-7410.

Sincerely,

John K. Jenkins, M.D., F.C.C.P.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

cc:
Archival NDA 20-971
HFD-170/Div. Files
HFD-170/SS/Moody (with labeling)
HFD-170/McCormick/Rappaport/Blatt (with labeling)
HFD-170/D'Sa/Maturu (with labeling)
HFD-170/Jean/Goheer
HFD-170/Permutt/Klein
HFD-700/Hu
HFD-160/Uranti
HFD-44/Askine/Abrams (with labeling)
HFD-344/Thomas/Snipes
HFD-002/ORM
HFD-103/ADRA
HFD-95/DDMS
HFD-40/DDMAC (with labeling)
HFD-820/DNDC Division Director
HFD-102/Jenkins (with labeling)
HFD-102/Ripper (with labeling)
HFD-103/Raczkowski (with labeling)
DISTRICT OFFICE

Drafted by: SS/May 6, 1999
Initialed by: C.P.Moody/May 6, 1999
final:
filename:20971.M06.AE

APPROVABLE (AE)

FAX
TRANSMISSION

DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS
5600 Fishers Lane
HFD-170, Rm. 9B-45
Rockville, Maryland 20857
Office: 301-827-7410
Fax: 301-480-8682/301-443-7068

To: MR. Wayne Matelski Date: 5-7-99

Fax #: 202-857-6395 Pages: 15 (INCLUDING THIS COVER SHEET)

From: Susmita Samanta

Subject: Articaine, NDA 20-971 Approvable letter

Comments:

PLEASE CALL (301) 827-7410 IF RE-TRANSMISSION IS NECESSARY

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NDA 20-971

Arent Fox
1050 Connecticut Avenue, NW
Washington, D.C. 20036-5339

MAY 7 1999

Attention: Wayne H. Matelski, J.D.
United States Agent for and Counsel to
Deproco, Inc. and Specialites Septodont

Dear Mr. Matelski:

Please refer to your pending March 30, 1998 New Drug Application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Septanest — (articaine hydrochloride 4% with Epinephrine 1/200,000 solution injection) and Septanest — (articaine hydrochloride 4% with Epinephrine 1/100,000 solution injection).

We acknowledge receipt of your submissions dated March 9, 1999 and May 4, 1999.

Your submission of March 9, 1999 constituted a complete response to our January 29, 1999 action letter.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following deficiencies:

1) Recently, the FDA conducted an inspection of your drug product manufacturing facility, Specialites Septodont, located at Saint Maur De Fosses, Paris, France for conformance with current good manufacturing practices (cGMP). The inspection report (5/5/1999) revealed that the performance of the facility is unacceptable at this time. The issues involve deviations from current good manufacturing practices. A satisfactory inspection will be required before this application may be approved.

2) The issue of overage has not been satisfactorily addressed. There is a 15% overage in the product for epinephrine. The —% loss in manufacturing has not been satisfactorily accounted for. Please provide documentation of decomposition products or other evidence of loss. Also, based on the —month stability data for three lots, the product can be granted a —month expiration date, not an —month expiration date (based on a —% overage) as you requested.

3) The product should be labeled with the epinephrine strength as it was formulated. Thus, you should report the epinephrine in ratios of 1.15:100,000 and 1.15:200,000 because the epinephrine amount is currently formulated with a 15% overage.

4) The proprietary name that you have proposed in response to the January 29, 1999, approvable letter continues to be unacceptable. The term "—" implies an original strength that was "weak". If that original strength were to be discontinued, the "—" part of the trademark could be misleading.

   Additionally, the agency has had numerous reports over the years of "—" being confused with the number "forty". Consequently, inappropriate doses or inappropriate numbers of doses of medication have been administered.

In addition, it will be necessary for you to submit revised draft labeling for the drug. The labeling should be identical in content to the enclosed labeling (text for the package insert).

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update your NDA by submitting all safety information you now have regarding your new drug. Please provide updated information as listed below. The update should cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels, etc.

1. Retabulation of all safety data including results of trials that were still ongoing at the time of NDA submission. The tabulation can take the same form as in your initial submission. Tables comparing adverse reactions at the time the NDA was submitted versus now will certainly facilitate review.

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7. Information suggesting a substantial difference in the rate of occurrence of common, but less serious, adverse events.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up

form, not final print. Please send one copy to the Division of Anesthetic, Critical Care, and Addiction Drug Products, HFD-170 and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal or telephone conference with the Division of Anesthetic, Critical Care, and Addiction Drug Products, HFD-170 to discuss what further steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, contact Susmita Samanta, Regulatory Project Manager, at 301-827-7410.

Sincerely,

/S/ FOR 5/7/99

John K. Jenkins, M.D., F.C.C.P.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

cc:
Archival NDA 20-971
HFD-170/Div. Files
HFD-170/SS/Moody (with labeling)
HFD-170/McCormick/Rappaport/Blatt (with labeling)
HFD-170/D'Sa/Maturu (with labeling) 5/7/99
HFD-170/Jean/Goheer
HFD-170/Permutt/Klein
HFD-700/Hu
HFD-160/Uranti
HFD-44/Askine/Abrams (with labeling)
HFD-344/Thomas/Snipes
HFD-002/ORM
HFD-103/ADRA
HFD-95/DDMS
HFD-40/DDMAC (with labeling)
HFD-820/DNDC Division Director
HFD-102/Jenkins (with labeling)
HFD-102/Ripper (with labeling)
HFD-103/Raczkowski (with labeling)
DISTRICT OFFICE

Drafted by: SS/May 6, 1999
Initialed by: C.P.Moody/May 6, 1999
final:
filename:20971.M06.AE

APPROVABLE (AE)

__11__ Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

__X__ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NDA 20-971

Arent Fox
1050 Connecticut Avenue, NW
Washington, D.C. 20036-5339

JAN 29 1999

Attention: Wayne H. Matelski, J.D.
United States Agent for and Counsel to
Deproco, Inc. and Specialities Septodont

Dear Mr. Matelski:

Please refer to your pending March 30, 1998 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Septanest— (articaine hydrochloride 4% with Epinephrine 1/200,000 solution injection) and Septanest—— (articaine hydrochloride 4% with Epinephrine 1/100,000 solution injection).

We acknowledge receipt of your submissions dated April 29, 1998, May 18, 1998, May 26, 1998, August 21, 1998, September 10, 1998, October 23, 1998, December 1, 1998, and December 4, 1998.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following:

1. Recently, our inspectors could not complete inspection of your _____ manufacturing facilities for conformance with current good manufacturing practices (cGMP) because the facilities were not ready for inspection. A satisfactory inspection will be required before this application may be approved.

2. Labeling on the cartridge must be imprinted with the following phrase "Contains sodium metabisulfite".

3. Assurance must be provided that the imprinting on the cartridge does not rub off with normal use.

4. The names "Septanest _____ are misleading by not revealing both ingredients, articaine and epinephrine. The brand names for these products will need to be revised accordingly. We suggest that the drug product's brand name be followed by the strength for both ingredients.

5. Include a limit for each specified impurity originating from articaine HCl and epinephrine tartrate and a limit for total impurities in the regulatory specifications for the drug product.

6. Update carton labeling to reflect new brand names. Indication on carton labeling should refer to package insert or read exactly as the package insert.

7. Overage for any product to merely extend the expiration dating is not allowed. Please label the product to reflect the epinephrine content. The recommended expiration dating period for the drug product is — months.

In addition, it will be necessary for you to submit final printed labeling (FPL) for the drug. The labeling should be identical in content to the enclosed labeling (text for the package insert, immediate container and carton labels).

Please submit 20 copies of the final printed labeling ten of which are individually mounted on heavy weight paper or similar material.

Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update your NDA by submitting all safety information you now have regarding your new drug. Please provide updated information as listed below. The update should cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels, etc.

1. Retabulation of all safety data including results of trials that were still ongoing at the time of NDA submission. The tabulation can take the same form as in your initial submission. Tables comparing adverse reactions at the time the NDA was submitted versus now will certainly facilitate review.

2. Retabulation of drop-outs with new drop-outs identified. Discuss, if appropriate.

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Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal or telephone conference with the Division of Anesthetic, Critical Care, and Addiction Drug Products, HFD-170 to discuss what further steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, contact Ken Nolan, Project Manager, at (301) 827-7410.

Sincerely,

Victor F.C. Raczkowski 1/29/99

Victor Raczkowski, M.D.
Acting Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

32 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

__X__ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

3 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

X § 552(b)(5) Deliberative Process