CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:
20-971/S009

Trade Name: Septocaine®

Generic Name: articaine hydrochloride; epinephrine bitartrate

Sponsor: Deproco, Inc.

Approval Date: 2/4/2005
## Reviews / Information Included in this NDA Review.

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APPLICATION NUMBER:
20-971/S009

APPROVAL LETTER
NDA 20-971/S-009

Arent Fox, PLLC
1050 Connecticut Avenue, N.W.
Washington, DC 20036-5339

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

Dear Mr. Matelski:

Please refer to your supplemental new drug application dated August 4, 2004, received August 5, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Septocaine® (Articaine Hydrochloride 4% (40 mg/mL) with Epinephrine 1:100,000 Injection).


This supplemental new drug application proposes to introduce a private-labeled version of the approved product under the trade name ZORCAINE.

We have completed our review of this application, as amended, and it is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text and with the following minor editorial revisions agreed upon during the February 3, 2005, teleconference:

1. You will ensure that the established name on the Container and Carton labels is at least ½ the size of the proprietary name per the requirements of CFR 201.10(g)(2).

2. You will revise the Carton label to include net quantity of each vial.

3. You will decrease the prominence of the name “Cook-Waite” on the Carton label as it appears more prominent than the proprietary and established names.

4. You will consider adding a barcode to each vial.

The final printed labeling (FPL) must be identical to the submitted labeling (text for the package insert submitted September 1, 2004, immediate container and carton labels submitted September 1, 2004).

Please submit an electronic version of the FPL according to the guidelines for industry titled Providing Regulatory Submissions in Electronic Format – NDA and Providing Regulatory Submissions in Electronic Format-Content of Labeling. Alternatively, except for the content of labeling, which must be submitted electronically in PDF format, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-
weight paper or similar material. For administrative purposes, designate this submission "FPL for approved supplement NDA 20-971/S-009." Approval of this submission by FDA is not required before the labeling is used.

We remind you that current and future promotional materials should be revised to reflect the new approved name, Zorcaine. Furthermore, we advise you to implement the aforementioned revision in a manner that does not imply that Zorcaine is a newly approved product.

If you issue a letter communicating important information about this drug product (i.e., a “Dear Health Care Professional” letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Allison Meyer, Regulatory Project Manager, at (301) 827-7431.

Sincerely,

{See appended electronic signature page}

Bob A. Rappaport, MD
Director
Division of Anesthetic, Critical Care, And Addiction Drug Products
Office of New Drugs 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/

---------------------
Bob Rappaport
2/4/05 03:12:57 PM
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
20-971/S009

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

ZORCAINE™ with epinephrine 1:100,000 injection contains articaine hydrochloride 4% (40 mg/mL) with epinephrine 1:100,000 in a preservative-free solution. Articaine HCl is a racemic mixture of (S)- and (R)-articaine. Articaine HCl is a member of the amino amide class of local anesthetics. Local anesthetics block the generation and propagation of neuronal electrical impulses by interference with the transmembrane movement of sodium ions during the upstroke phase of action potentials. Sodium channels are selectively blocked, which reduces the amplitude of propagated action potentials. This reduction in amplitude interferes with nerve transmission and produces a loss of sensation. 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. Epinephrine's vasoconstrictive action is greatest at the arteries and smallest at the capillaries. Epinephrine is also able to increase the contractility of the heart and reduce peripheral vasodilation. Prostaglandin E1 may be useful in increasing the rate of absorption of the injectate when used in conjunction with a local anesthetic. The upregulated prostaglandin E1 receptors are capable of mediating increased vasoconstriction, which in turn increases the rate of absorption of the injected solution.

**Description**

Articaine HCl is rapidly metabolized by plasma carboxyesterase to its primary metabolite, articainic acid, which is further oxidized in the human liver microsome P450 isoenzyme system metabolizes approximately 5% to 10% of available articaine with nearly complete recovery (Kaplan, EL, editor: Cardiovascular Anesthesia. Philadelphia: FA Davis; 1980:579-585). Articaine HCl is a member of the amino amide class of local anesthetics. Local anesthetics block the generation and propagation of neuronal electrical impulses by interference with the transmembrane movement of sodium ions during the upstroke phase of action potentials. Sodium channels are selectively blocked, which reduces the amplitude of propagated action potentials. This reduction in amplitude interferes with nerve transmission and produces a loss of sensation. 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. Epinephrine's vasoconstrictive action is greatest at the arteries and smallest at the capillaries. Epinephrine is also able to increase the contractility of the heart and reduce peripheral vasodilation. Prostaglandin E1 may be useful in increasing the rate of absorption of the injectate when used in conjunction with a local anesthetic. The upregulated prostaglandin E1 receptors are capable of mediating increased vasoconstriction, which in turn increases the rate of absorption of the injected solution.

**Pharmacokinetics**

Articaine HCl is rapidly metabolized by plasma carboxyesterase to its primary metabolite, articainic acid, which is further oxidized in the human liver microsome P450 isoenzyme system metabolizes approximately 5% to 10% of available articaine with nearly complete recovery (Kaplan, EL, editor: Cardiovascular Anesthesia. Philadelphia: FA Davis; 1980:579-585). Articaine HCl is a member of the amino amide class of local anesthetics. Local anesthetics block the generation and propagation of neuronal electrical impulses by interference with the transmembrane movement of sodium ions during the upstroke phase of action potentials. Sodium channels are selectively blocked, which reduces the amplitude of propagated action potentials. This reduction in amplitude interferes with nerve transmission and produces a loss of sensation. 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. Epinephrine's vasoconstrictive action is greatest at the arteries and smallest at the capillaries. Epinephrine is also able to increase the contractility of the heart and reduce peripheral vasodilation. Prostaglandin E1 may be useful in increasing the rate of absorption of the injectate when used in conjunction with a local anesthetic. The upregulated prostaglandin E1 receptors are capable of mediating increased vasoconstriction, which in turn increases the rate of absorption of the injected solution.

**Absorption**

The systemic availability of articaine HCl is dependent upon the route of administration. Following subcutaneous or intramuscular injection, articaine HCl is rapidly absorbed into the circulation. The absorption rate is influenced by systemic blood flow. Peak blood concentrations following subcutaneous or intramuscular injection are typically reached within 0-15 minutes and are usually less than 100 ng/mL. Articaine HCl is rapidly distributed to the tissues, with peak tissue concentrations typically reached within 30-60 minutes. Following intravenous injection, articaine HCl is rapidly distributed to the tissues and peak blood concentrations are typically reached within 1-5 minutes. Following oral administration, articaine HCl is rapidly absorbed into the circulation and peak blood concentrations are typically reached within 30-60 minutes. Following sublingual or buccal administration, articaine HCl is rapidly absorbed into the circulation and peak blood concentrations are typically reached within 30-60 minutes.

**Distribution**

Articaine HCl is rapidly distributed throughout the body. Following subcutaneous or intramuscular injection, articaine HCl is rapidly absorbed into the circulation. The absorption rate is influenced by systemic blood flow. Peak blood concentrations following subcutaneous or intramuscular injection are typically reached within 0-15 minutes and are usually less than 100 ng/mL. Articaine HCl is rapidly distributed to the tissues, with peak tissue concentrations typically reached within 30-60 minutes. Following intravenous injection, articaine HCl is rapidly distributed to the tissues and peak blood concentrations are typically reached within 1-5 minutes. Following oral administration, articaine HCl is rapidly absorbed into the circulation and peak blood concentrations are typically reached within 30-60 minutes. Following sublingual or buccal administration, articaine HCl is rapidly absorbed into the circulation and peak blood concentrations are typically reached within 30-60 minutes. Following oral administration, articaine HCl is rapidly absorbed into the circulation and peak blood concentrations are typically reached within 30-60 minutes.

**Excretion**

Articaine HCl is excreted predominantly by the kidney. Following subcutaneous or intramuscular injection, articaine HCl is rapidly absorbed into the circulation. The absorption rate is influenced by systemic blood flow. Peak blood concentrations following subcutaneous or intramuscular injection are typically reached within 0-15 minutes and are usually less than 100 ng/mL. Articaine HCl is rapidly distributed to the tissues, with peak tissue concentrations typically reached within 30-60 minutes. Following intravenous injection, articaine HCl is rapidly distributed to the tissues and peak blood concentrations are typically reached within 1-5 minutes. Following oral administration, articaine HCl is rapidly absorbed into the circulation and peak blood concentrations are typically reached within 30-60 minutes. Following sublingual or buccal administration, articaine HCl is rapidly absorbed into the circulation and peak blood concentrations are typically reached within 30-60 minutes. Following oral administration, articaine HCl is rapidly absorbed into the circulation and peak blood concentrations are typically reached within 30-60 minutes.


**ADVERSE REACTIONS**

No overall differences in safety or effectiveness were observed between elderly subjects and younger subjects, and other indications of increased sensitivity of some older individuals cannot be ruled out.

**Phenothiazines and butyrophenones may reduce or reverse the pressor effect of epinephrine. Concurrent use of these agents should generally be avoided.**

In situations when concurrent therapy is necessary, careful patient monitoring is essential.

**OVERDOSAGE**

The first consideration is prevention, best accomplished by careful and constant monitoring of cardiovascular and respiratory function before, during, and after administration of ZORCAINE. Cardiac and respiratory vital signs and the patient's state of consciousness after each local anesthetic injection should be assessed.

At the first sign of change, oxygen should be administered. The adequacy of the circulation should be assessed. Should convulsions persist despite adequate respiratory support, treatment with diazepam (Valium®) or similar drugs may be required. Phenytoin (Dilantin®) may be useful in controlling convulsions in certain situations.

**Acute emergencies from local anesthetics are generally related to high plasma levels encountered during therapeutic use of local anesthetics or to unintended overdosage in patients with diminished capacity for drug inactivation.**

**Mammalian gene mutation test and a chromosomal aberration test** and a mammalian gene mutation test with articaine HCl) and two in vivo mouse micronucleous tests (one with ZORCAINE with epinephrine 1:100,000 and one with articaine HCl alone) showed no mutagenic effects. No effects on male or female fertility were observed in these studies.

**Dosing**

**Pediatric Use**

Use in pediatric patients under 4 years of age is recommended. The quantity to be injected should be determined by the age and weight of the child and the magnitude of the operation. For children of less than 10 years who have a normal lean body mass and normal body development, the maximum dose may be determined by the following formula: V (mL) = 2.5 (kg of body weight). In children under 10 years of age who are larger than average for their age or who are more overweight, the maximum dose may be determined by an increased body surface area. The dose should be approximately 0.15 mg/kg or 0.5 mL/kg of body weight or the following formula: V (mL) = 0.3 (kg of body weight) + 0.5 mL/kg of body weight.

**General Considerations**

If not treated immediately, both convulsions and cardiovascular depression can result in hypoxia, acidosis, bradycardia, arrhythmias and cardiac arrest. Efforts should be directed toward respiratory stimulation, circulatory support, and specific measures to counteract hypoxia, acidosis, and arrhythmias. Treatment of circulatory depression may require administration of IV fluids and, when appropriate, a vasopressor.

If patients show any signs of acute anaphylactic or anaphylactoid reaction, treat with epinephrine and, if necessary, with a combination of antihistamines and corticosteroids. If the patient shows signs of respiratory depression, treatment with 100% oxygen, by mask or intubation if necessary, should be started immediately.

In the event of an anaphylactoid or anaphylactic reaction, intramuscular or subcutaneous injection of 0.1 mL of 1:1000 epinephrine (0.1 mg of adrenaline) should be administered. Further treatment should be determined by the clinical response of the patient and the presence or absence of other complications. For more detailed information on the treatment of anaphylactoid reactions, see the appropriate references.

**Storage**

Store at controlled room temperature, below 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. DO NOT PERMIT TO FREEZE.

**HOW SUPPLIED**

For chemical disinfection of the carpule, ether isopropyl alcohol (91%) or ethyl alcohol (70%) is recommended. Many commercially available brands of isopropyl (rubbing) alcohol, as well as ethyl alcohol, have been used successfully for chemical disinfection of the carpule. For disinfection of the syringes and needles, ethyl alcohol (70%) or isopropyl alcohol (91%) is recommended.
MEDICAL REVIEW(S)
Executive Summary:

The sponsor proposes to introduce a private-labeled version of the approved product, Septocaine, a local anesthetic used in dentistry, under the trade name Zorcaine. Septocaine was approved on April 3, 2000. Zorcaine is to be manufactured in Canada and distributed in The United States by Eastman Kodak Company.

Consultation for the submitted labeling change was obtained from the Division of Medication Errors and Technical Support and the Division of Drug Marketing, Advertising and Communications (Tea Harper-Velazquez, Alina Mahmud and Carol Holquist). Nine other approved products were considered for potential name confusion with Zorcaine. The consultants’ safety evaluation and risk assessment concluded that the sponsor’s request to use the name “Zorcaine” for their Articaine Hydrochloride/Epinephrine Injection, 4%/1:100,000 product is acceptable.

The consultants also made several suggestions to change the product labeling.

The sponsor’s submission to use the name Zorcaine should be approved with modifications to the product labeling as suggested by the Office of Drug Safety.

1 Background

The consultant divisions conducted a search of published drug reference texts, Agency and commercial databases for existing drugs with similar sounding or appearing names. Nine products were identified consisting of Marcaine, Sensorcaine, Novocaine, Zovirax, Soriatane, Zocor, Psorcon, Psorcon-E, and Septocaine. The Division of Medication Errors and Technical Support (DMETS) also conducted prescription analysis studies with the nine similar sounding/appearing drugs to evaluate potential confusion when ordering Zorcaine. An Expert Panel convened to review professional opinions on
the safety of the proposed proprietary name, Zorccaine determined that the proposed name was acceptable. The Division of Drug Marketing, Advertising and Communications also indicated that there were no outstanding concerns from a promotional perspective regarding the proposed name.

DMETS identified several areas of labeling that may be changed to minimize potential user error. These are:

A. Container Label
   1. Change the size of the established name to be at least ½ the size of the proprietary name.

   2. Increase the prominence of the product strength as follows:
      Articaine Hydrochloride       4%
      with Epinephrine                  1:100,000
      Injection

      or

      Articaine Hydrochloride with Epinephrine Injection
      4%/1:100,000

   3. Include the route of administration on the container label, if space permits.

B. Carton Label
   1. Increase the size of the established name to the proprietary name as suggested for the container label. Increase the prominence of the product strength as suggested for the container label.

   2. Include a net quantity statement.

   3. Decrease the prominence of the manufacturer name so that it appears less prominent than the proprietary and established names.

C. Package Insert Labeling
   in the table in the DOSAGE AND ADMINISTRATION section.

2  Review of proposed labeling change

   There do not appear to be safety concerns associated with the proposed name that would result in confusion with other products.

3  Recommendations:
The sponsor’s submission to use the name Zorcaine should be approved with modifications to the product labeling as suggested by the Office of Drug Safety.

Changes to the Container, Carton and Package Insert labeling suggested by DMETS may be helpful. The suggestion to increase the size of the established name to be at least ½ the size of the proprietary name is supported by 21 CFR 201.10 (g)(2) and should be implemented.

Lex Schultheis, MD, Ph.D.
Medical Officer

CC: HFD-170 Division File
HFD-170:
Lex Schultheis, MD, Ph.D.
Rigoberto Roca, M.D.
Bob Rappaport, MD
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Lester Schultheis
2/2/05 03:06:06 PM
MEDICAL OFFICER

Bob Rappaport
2/2/05 05:25:01 PM
MEDICAL OFFICER
APPLICATION NUMBER:
20-971/S009

OTHER REVIEW(S)
Background and Summary: The sponsor has proposed to introduce a private-labeled version of the approved product under the trade name ZORCAINE. The proposed labeling was reviewed by the Division of Medication Errors and Technical Support and found acceptable.

Review

As per telephone conversation with the sponsor on February 3, 2003, the following agreements were reached for changes in the label as suggested by the Division of Medication Errors and Technical Support:

A. Container Label
   • Ensure that the established name is at least ½ the size of the proprietary name per CFR 201.10(g)(2).
   • Consider including a barcode on each vial.

B. Carton Label
   • Ensure that the established name is at least ½ the size of the proprietary name per CFR 201.10(g)(2).
   • Include a net quantity statement (add term each).
   • Decrease the prominence of the name “Cook-Waite” as it appears more prominent than the proprietary and established names.
There is a change noted in the Proprietary name from Septocaine to Zorcaine.

Allison Meyer
Regulatory Project Manager

Supervisory Comment/Concurrence:

Parinda Jani
Chief, Project Management Staff

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

/s/
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Allison Meyer
2/3/05 10:56:33 AM
CSO

Parinda Jani
2/3/05 02:21:51 PM
CSO
## CONSULTATION RESPONSE
### DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
### OFFICE OF DRUG SAFETY
### (DMETS; HFD-420)

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<th>DESIRED COMPLETION DATE:</th>
<th>October 20, 2004</th>
<th>ODS CONSULT #:</th>
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### TO:
Bob Rappaport, M.D.
Director, Division of Anesthetic, Critical Care and Addiction Drug Products
HFD-170

### THROUGH:
Allison Meyer
Project Manager, Division of Anesthetic, Critical Care, and Addiction Drug Products
HFD-170

### PRODUCT NAME:
Zorcaine
(Articaine Hydrochloride/Epinephrine Injection)
4%/1:100,000

### SPONSOR:
Deproco, Inc.

### NDA #: 20-971/S-009

### SAFETY EVALUATOR:
Tia M. Harper-Velazquez, Pharm.D.

### RECOMMENDATIONS:

1. DMETS has no objections to the use of the proprietary name, Zorcaine. This is considered a final decision. However, if the approval of this application is delayed beyond 90 days from the signature date of this document, the name must be re-evaluated. A re-review of the name will rule out any objections based upon approval of other proprietary or established names from the signature date of this document.

2. DMETS recommends implementation of the label and labeling revisions outlined in Section III of this review in order to minimize potential errors with the use of this product.

3. DDMAC finds the proprietary names Zorcaine acceptable from a promotional perspective.

---

Carol Holquist, R.Ph.
Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242   Fax: (301) 443-9664
DATE OF REVIEW: September 29, 2004

NDA NUMBER: 20-971/S-009

NAME OF DRUG: Zorcaine
(Articaine Hydrochloride/Epinephrine Injection)
4%/1:100,000

NDA SPONSOR: Deproco, Inc.

I. INTRODUCTION

This consult was written in response to a request from the Division of Anesthetic, Critical Care and Addiction Drug Products for an assessment, of the proprietary name “Zorcaine” regarding potential name confusion with other proprietary or established drug names. The sponsor submitted this trade name review as part of a supplement application, which proposes to introduce a private-labeled version of the approved drug product, Septocaine, under the trade name, Zorcaine. Septocaine was approved on April 3, 2000, under NDA 20-971. Zorcaine will be manufactured in Canada, and distributed in the United States by Eastman Kodak Company. Container labels, carton and insert labeling were provided for review and comment.

PRODUCT INFORMATION

Zorcaine is the proposed name for a combination drug product containing articaine in a strength of 4% and epinephrine in a concentration of 1:100,000. It is indicated for local, infiltrative, or conductive anesthesia in both simple and complex dental and periodontal procedures. The maximum dose should not exceed 7 mg/kg (0.175 mL/kg) or 3.2 mg/lb (0.0795 mL/lb) of body weight. Zorcaine will be provided in 1.7 mL glass cartridges, in boxes of 50 cartridges.

II. RISK ASSESSMENT

The medication error staff of DMETS conducted a search of several standard published drug product reference texts\(^i\) as well as several FDA databases\(^ii\) for existing drug names which sound-alike or look-alike to “Zorcaine” to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent

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\(^ii\) Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

\(^iii\) AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support proprietary name consultation requests, New Drug Approvals 1998-2004, and the electronic online version of the FDA Orange Book.
and Trademark Office’s Text and Image Database\textsuperscript{iv} and the data provided by Thomson & Thomson’s SAEGIS\textsuperscript{TM} Online Service\textsuperscript{v} were also conducted. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name, Zorcaine. Potential concerns regarding drug marketing and promotion related to the proposed name was also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC did not have any concerns from a promotional perspective regarding the proposed name Zorcaine.

2. The Expert Panel identified nine proprietary names that have potential for confusion with Zorcaine. These products are listed in Table 1 along with the dosage forms available and usual dosage (see pages 4 and 5).

\textsuperscript{iv} WWW location http://www.uspto.gov.

\textsuperscript{v} Data provided by Thomson & Thomson’s SAEGIS(tm) Online Service, available at www.thomson-thomson.com.
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<th>Product Name</th>
<th>Dosage form(s), Established name</th>
<th>Usual adult Dose*</th>
<th>Other **</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zorcaine (Rx)</td>
<td>Articaine/Epinephrine Injection 4%/1:100,000</td>
<td>**</td>
<td></td>
</tr>
<tr>
<td>Marcaine (Rx) and Sensorcaine (Rx)</td>
<td>Bupivicaine Injection 0.25%, 0.5%, 0.75% and Bupivicaine/Epinephrine 0.25%/1:200,000, 0.5%/1:200,000, 0.75%/1:200,000, and 0.75%/1:200,000</td>
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<tr>
<td>Novocaine (Rx)</td>
<td>Procaine Injection 1%, 2%, and 10%</td>
<td>Infiltration anesthesia: 350 mg to 600 mg of a 0.25% to 0.5% solution. Peripheral nerve block: Up to 200 mL of a 0.5% solution or up to 50 mL of a 2% solution. Spinal anesthesia</td>
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<tr>
<td>Zovirax (Rx)</td>
<td>Acyclovir Capsules: 200 mg Tablets: 400 mg and 800 mg Suspension: 200 mg/5 mL</td>
<td>Give 200 mg every 4 hours (5 times daily) for ten days. For chronic treatment give 400 mg 2 times daily of 200 mg 3-5 times daily for up to 12 months.</td>
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<td>Soriatane (Rx)</td>
<td>Acitretin Capsules 10 mg and 25 mg</td>
<td>Take 25 mg to 50 mg once daily with main meal.</td>
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<td>Zocor (Rx)</td>
<td>Simvastatin Tablets 5 mg, 10 mg, 20 mg, 40 mg, and 80 mg</td>
<td>Take 20 mg to 40 mg once daily in the evening.</td>
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### Table

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<tr>
<th>Product Name</th>
<th>Dosage form(s), Established name</th>
<th>Usual adult Dose*</th>
<th>Other **</th>
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<tr>
<td>Zorcare (Rx)</td>
<td>Articaine/Epinephrine Injection 4%/1:100,000</td>
<td><img src="image" alt="Dose Table" /></td>
<td>Maximum dose should not exceed 7 mg/kg (0.175 mL/kg) or 3.2 mg/lb (0.0795 mL/lb) of body weight.</td>
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<tr>
<td>Psorcon (Rx)</td>
<td>Diflorasone Ointment 0.05%</td>
<td><strong>Apply a thin film 1 to 3 times daily.</strong></td>
<td><strong>S/A</strong></td>
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<td>Psorcon-E (Rx)</td>
<td>Diflorasone Emollient Cream 0.05%</td>
<td><strong>Apply a thin film 1 to 3 times daily.</strong></td>
<td><strong>S/A</strong></td>
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<td>Septoaine (Rx)</td>
<td>Articaine/Epinephrine Injection 4%/1:100,000</td>
<td><img src="image" alt="Dose Table" /></td>
<td>Maximum dose should not exceed 7 mg/kg (0.175 mL/kg) or 3.2 mg/lb (0.0795 mL/lb) of body weight.</td>
</tr>
</tbody>
</table>

*Frequently used, not all-inclusive.
**L/A (look-alike), S/A (sound-alike)

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**B. PHONETIC ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)**

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary names were converted into their phonemic representation before they run through the phonetic algorithm. The phonetic search modules return a numeric score to the search engine based on the phonetic similarity to the input text. Likewise, an orthographic algorithm exists which operates in a similar fashion. All names considered to have significant phonetic or orthographic similarities to Zorcare were discussed by the Expert Panel (EPD).

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**C. AERS AND DQRS DATABASE RESEARCH**

DMETS searched the FDA Adverse Event Reporting System (AERS) and the Drug Quality Reporting System (DQRS) database in order to identify any post-marketing safety cases of medication errors associated with products ending with the “caine”. AERS was searched for domestic cases using the MedDRA Preferred Terms of “Medication Error”, “Overdose”, “Accidental Overdose,” “Pharmaceutical Product Complaint,” and drug names of Septoaine, Marcare, Sensorcare, Novocaine, Soritane, Bupivicane, Procare, Lidocaine, and Articaine. Upon omitting duplicates, a total of forty-four reports were identified. One case involved name confusion due to look-alike similarities between ropivacaine and bupivacaine, in which a nurse re-writing medication orders transcribed the drug name ropivacaine incorrectly. The remaining cases involved incidences of mislabeling by pharmacy personnel due to miscommunication, incorrect technique (due to catheter migration, and inappropriately administering the drug in conjunction
with unintended drug products), similarities in labels and labeling of an unknown product line with multiple strengths, wrong patient, wrong route of administration, inadequate drug effect, as well as incorrect product selection due to look-alike vials of Marcaine in the Sanofi-Winthrop Pharmaceuticals product line, look-alike vials of Sensorcaine in the Astra-Zeneca product line, and look-alike vials of Marcaine (bupivacaine) in the Abbott product line. Upon further research, DMETS learned that due to company mergers, Sanofi-Winthrop Pharmaceuticals no longer exists, and was merged into Sanofi-Aventis. In addition, Marcaine injection, manufactured by either Sanofi-Winthrop or Sanofi-Aventis, does not appear in the 2004 edition of the Red Book, thus minimizing the concern due to look-alike vials in this product line. Errors pertaining to Marcaine and Marcaine with Epinephrine in the Abbott/Hospira product lines have been previously addressed in a post-marketing consult by DMETS. Issues concerning the similarities in labels in the Astra-Zeneca product line will be addressed in a separate post-marketing review.

D. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within the centers of the FDA for the proposed proprietary names to determine the degree of confusion of Zorcaine with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 129 health care professionals (pharmacists, physicians, and nurses) for each name. This exercise was conducted in an attempt to simulate the prescription ordering process. Two pharmacy requisitions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Zorcaine (see below). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the requisition orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving the requisition prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

<table>
<thead>
<tr>
<th>HANDWRITTEN PRESCRIPTION</th>
<th>VERBAL PRESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacy Requisition:</td>
<td>Zorcaine Injection, #6, order code ZCH.</td>
</tr>
<tr>
<td>60</td>
<td>2 CH</td>
</tr>
<tr>
<td>Pharmacy Requisition:</td>
<td></td>
</tr>
<tr>
<td>60</td>
<td>2 CH</td>
</tr>
</tbody>
</table>
2. Results:

None of the interpretations of the proposed name overlap, sound similar, or look similar to any currently marketed U.S. product. See appendix A for the complete listing of interpretations from the verbal and written studies.

E. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name “Zorcaine”, the primary concerns were related to nine look-alike and/or sound-alike names currently marketed in the United States. The products considered to have potential for name confusion with Zorcaine were: Marcaine, Sensorcaine, Novocaine, Zovirax, Soriatane, Zocor, Psorcon, Psorcon-E, and Septocaine. Upon further review of the names gathered from EPD and POCA, the names Zovirax, Soriatane, Zocor, Psorcon, and Psorcon-E were not reviewed further due to a lack of convincing look-alike and sound-alike similarities with Zorcaine, in addition to numerous differentiating product characteristics such as product strength, indication for use, context of use, route of administration, and dosage formulation.

We conducted prescription studies to simulate the prescription ordering process. Our study did not confirm confusion between Zorcaine and Marcaine, Sensorcaine or Novocaine. However, a negative finding does not discount the potential for name confusion given the limited predictive value of these studies, primarily due to the sample size. The majority of the incorrect interpretations of the written and verbal studies were misspelled/phonetic variations of the proposed name, Zorcaine.

1. Marcaine was identified to look and sound similar to the proposed name, Zorcaine. Marcaine contains the active ingredient bupivacaine, and is available with or without epinephrine. It is indicated as a local anaesthetic, which can be used for techniques including local infiltration, minor and major nerve blocks, epidural block and arthroscopy. The recommended dose varies depending on the procedure, and the type of block necessary. Both names consist of eight letters, two syllables, and the first two letters of each name can look similar when scripted (“Ma” vs. “Zo”). The remaining letters “rcaine” appear in both names, in the same order, which adds to the orthographic and phonetic similarity. There is, however, a difference between the sounds of the letters “M” and “Z” which helps to distinguish the beginning of the names from each other when spoken. Marcaine and Zorcaine also share an overlapping route of administration (intravenous), dosage form (injection), indication of use (anesthesia), and potential dosing strength. The products differ in strength (4%/1:100,000 vs. 0.25%/1:200,000, 0.5%/1:200,000, and 0.75%/1:200,000). Because Zorcaine will be available in only one strength, Zorcaine can be ordered and dispensed without a strength being indicated, whereas a strength must be indicated prior to dispensing Marcaine since it is available in multiple strengths. Although the names share some orthographic similarities, and have a rhyming quality, DMETS believes that the differences in product strength will minimize the potential for confusion between the two products.
2. Sensorcaine was identified to sound similar to Zorcaine. Like Marcaine, Sensorcaine contains the active ingredient bupivicaine, and is available with or without epinephrine. It is indicated as a local anaesthetic, which can be used for techniques including local infiltration, minor and major nerve blocks, epidural block and arthroscopy. The sound-alike similarity between the names can be attributed to the letters “sor” in Sensorcaine which are phonetically similar to the proposed name, Zorcaine. However, the names differ in number of syllables (two vs. three), and the presence of the letters “Sen” at the beginning of Sensorcaine helps to distinguish the names from each other when spoken. Sensorcaine and Zorcaine share an overlapping route of administration (intravenous), dosage form (injection), indication of use (anesthesia), and potential dosing strength. The products differ in strength (4%/1:100,000 vs. 0.25%/1:200,000, 0.5%/1:200,000, and 0.75%/1:200,000). In addition, because it will be available in only one strength Zorcaine can be ordered without a strength being indicated, whereas a strength must be indicated prior to dispensing Marcaine. The differences in the sound-alike similarities between the names, in addition to the differences in product strength make it unlikely that there will be confusion between Sensorcaine and Zorcaine.

3. Novocaine was identified to look and sound similar to the proposed name, Zorcaine. Novocaine contains procaine. It is indicated for infiltration anesthesia, peripheral nerve block, and spinal anesthesia. The recommended dose varies depending on the surgical procedure. The look-alike and sound-alike similarities between the names can be attributed to the letters “caine” which appear at the end of each name. In addition, the letters “No” in Novocaine and “Zo” in Zorcaine can look similar, depending on how they are scripted. The names differ in number of syllables (three vs. two), and phonetically, the beginning of the names are distinguishable from each other (“Novo” vs. “Zor”). Novocaine and Zorcaine share an overlapping route of administration (intravenous), dosage form (injection), indication of use (anesthesia), and potential dosing strength. For example, a patient who weighs 79 kg (180 lbs), receiving Zorcaine at a dose calculation of 7 mg/kg, would receive a total dose of 553 milligrams of Zorcaine. This falls within the dosing parameters for Marcaine of 350 mg to 600 mg for infiltration anesthesia. However, the products differ in strength (1%, 2% and 10% vs. 4%/1:200,000). In addition, because Zorcaine will be available in a single strength, prescriptions can be ordered without a strength being indicated, whereas a strength must be indicated prior to dispensing Novocaine, since it is available in multiple strengths. DMETS believes that the lack of convincing look-alike and sound-alike similarities between the names, in addition to the differences in product strength, make it unlikely that Novocaine and Zorcaine will be confused for one another.

4. Septocaine was identified to sound similar to the proposed name, Zorcaine. Like Zorcaine, Septocaine contains the active ingredients articaine hydrochloride and epinephrine in a strength of 4%/1:100,000, and has the same dosing schedule. The sound-alike similarities between the names can be attributed to the identical endings (“caine”). However, the beginnings of the names are phonetically distinguishable from each other (“Septo” vs. “Zor”). Additionally, if a prescription order for Zorcaine is filled with Septocaine, and vice versa, it is not likely that a patient would experience harm because both products contain the same active ingredient, and have identical strengths and dosing regimen. Despite the overlapping product characteristics, DMETS believes
that the proprietary names Septocaine and Zorcaine can exist in the marketplace together due to the minimal sound-alike similarities between the names, in addition to the fact should confusion between the product names occur, this would not result in patient harm.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES

In review of the container labels, carton and insert labeling for Zorcaine, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified the following areas of possible improvement, which might minimize potential user error.

A. CONTAINER LABEL

1. Please ensure that the established name is at least ½ the size of the proprietary name, per 21 CFR 201.10(g)(2).

2. Please increase the prominence of the product strength. In addition, revise the established name and strength to appear as follows:

   Articaine Hydrochloride  4%
   with Epinephrine  1:100,000
   Injection
   or
   Articaine Hydrochloride with Epinephrine Injection
   4%/1:100,000

3. If space permits, please include the route of administration on the container label.

B. CARTON LABELING


2. Please include a net quantity statement.

3. Please decrease the prominence of the manufacturer name as it appears more prominent than the proprietary and established names.

C. PACKAGE INSERT LABELING

Delete trailing zeros appearing in the table in the DOSAGE AND ADMINISTRATION section.
IV. RECOMMENDATIONS

A. DMETS has no objections to the use of the proprietary name, Zorcaine. This is considered a final decision. However, if the approval of this application is delayed beyond 90 days from the signature date of this document, the name must be re-evaluated. A re-review of the name will rule out any objections based upon approval of other proprietary or established names from the signature date of this document.

B. DMETS recommends implementation of the label and labeling revisions outlined in Section III of this review in order to minimize potential errors with the use of this product.

C. DDMAC finds the proprietary names Zorcaine acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult (e.g., copy of revised labels/labeling). We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Sammie Beam at 301-827-3242.

Tia M. Harper-Velazquez, Pharm.D.
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur

Alina Mahmud, R.Ph.
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety
Appendix A. DMETS Prescription Study Results for Zorcaine

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/s/
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Tia Harper-Velazquez
12/23/04 09:34:05 AM
DRUG SAFETY OFFICE REVIEWER

Alina Mahmud
12/23/04 11:05:51 AM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
12/23/04 12:08:43 PM
DRUG SAFETY OFFICE REVIEWER
ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS
MEMORANDUM OF TELECON

DATE: February 3, 2005

APPLICATION NUMBER: NDA 20-971 / S-009

BETWEEN:

Name: Brian Waldman
Phone: 202-857-8971
Representing: Deproco, Inc.

AND

Name: Allison Meyer
Parinda Jani
Division of Anesthetic, Critical Care, and Addiction Drug Products,
HFD-170

SUBJECT: N20-971/S-009 Label

As per telephone conversation with the sponsor on February 3, 2003, the following agreements were reached for changes in the label as suggested by the Division of Medication Errors and Technical Support:

A. Container Label
   • Ensure that the established name is at least ½ the size of the proprietary name per CFR 201.10(g)(2).
   • Consider including a barcode on each vial.
B. Carton Label
   • Ensure that the established name is at least ½ the size of the proprietary name per CFR 201.10(g)(2).
   • Include a net quantity statement (add term each after 50 cartridges 1.7 mL).
   • Decrease the prominence of the name “Cook-Waite” as it appears more prominent than the proprietary and established names

________________________________________
SIGNER’S NAME
TITLE
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

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Allison Meyer
2/3/05 10:54:04 AM
CSO
# REQUEST FOR CONSULTATION

**TO (Division/Office):** HFD-420/Director, Division of Medication Errors and Technical Support; PKLN Rm. 6-34  
**FROM:** HFD-170 Division of Anesthetic, Critical Care and Addiction Drug Products  
**DATE:** August 16, 2004  
**IND NO.:**  
**NDA NO.:** 20-971  
**TYPE OF DOCUMENT:** Proposed Proprietary (Trade) Name  
**DATE OF DOCUMENT:** August 4, 2004  
**NAME OF DRUG:** Septocaine  
**PRIORITY CONSIDERATION:** n/a  
**CLASSIFICATION OF DRUG:**  
**DESIRED COMPLETION DATE:** October 16, 2004  
**NAME OF FIRM:** Deproco, Inc.  

**Comments/Special Instructions:** Review Of Tradename And Carton/Container Labels  

**Proposed Proprietary Name:** Zorcaine  
**Trademark registration status/Countries registered (if known):** US and Canada  
**Company Tradename:** Novocol Pharmaceutical of Canada, Inc.  
**Other proprietary names by same firm for companion products:** None  
**United States Adopted Name, dosage form, strength and dosing schedule:** Septocaine  
**Indication for use:** For infiltration or never block anesthesia in dentistry  
This consult will be accompanied by manual copies of the labeling.

**Signature of Requester:** Allison Meyer  
**Regulatory Project Manager**  
**Signature of Deliverer:**  
827-7431  
**Signature of Receiver:**  
**Signature of Deliverer:**
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
8/24/04 08:57:51 AM
NDA 20-971/S-009

Prior Approval Supplement

Arent Fox, PLLC
1050 Connecticut Avenue, N.W.
Washington, DC 20036-5339

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

Dear Mr. Matelski:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Septocaine® (Articaine Hydrochloride 4% (40 mg/mL) with Epinephrine 1:100,000 Injection)

NDA Number: 20-971

Supplement number: 009

Date of supplement: August 4, 2004

Date of receipt: August 5, 2004

This supplemental application proposes to introduce a private-labeled version of the approved product under the trade name ZORCAINE.

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service:
Center for Drug Evaluation and Research
Division of Anesthetic, Critical Care, and Addiction Drug Products, HFD-170
Attention: Document Room 8B-45
5600 Fishers Lane
Rockville, Maryland 20857
If you have any question, call me, at (301) 827-7431.

Sincerely,

{See appended electronic signature page}

Allison Meyer
Regulatory Project Manager
Division of Anesthetic, Critical Care and Addiction Drug 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/

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Allison Meyer
8/11/04 09:08:06 AM