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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-971/S009

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Reviews / Information Included in this NDA Review.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

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).

We acknowledge receipt of your submissions dated August 25, and September 1, 2004, and September 2, 2005.

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 guidances 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

Cook-Waite

Zorcaine™ with epinephrine 1:100,000

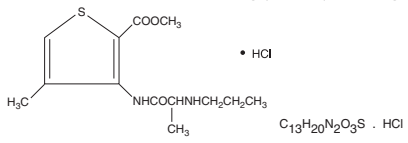
(articaine hydrochloride 4% (40 mg/mL) with epinephrine 1:100,000 injection)

Articaine hydrochloride 4% (40 mg/mL) with epinephrine 1:200,000 injection

For Inf ltration and Nerve Block Anesthesia

DESCRIPTION

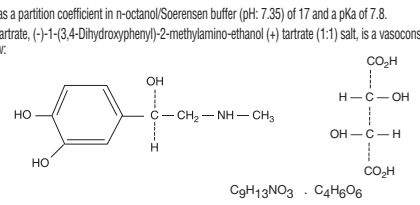
ZORCAINE with epinephrine 1:100,000 injection and articaine hydrochloride 4% with epinephrine 1:200,000 injection are ster le, aqueous solutions that contain articaine HCl 4% (40mg/mL) with epinephrine bitartrate in a 1:100,000 or 1:200,000 strength, respectively. Articaine HCl is a local anesthetic, 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 or 1:200,000 as the free base. It has a molecular weight of 333.3. The molecular and structural formulae are displayed below:



$C_9H_{13}NO_3$. $C_4H_6O_6$

ZORCAINE with epinephrine 1:100,000 injection and articaine hydrochloride 4% with epinephrine 1:200,000 injection contain articaine HCl (40 mg/mL), epinephrine as bitartrate (1:100,000 or 1:200,000, respectively), sodium chloride (1.6 mg/mL), and sodium metabisu f te (0.5 mg/mL). The products are formulated with a 15% overage of epinephrine. The pH is adjusted with sodium hydroxide.

CLINICAL PHARMACOLOGY

Pharmacokinetics

Absorption: Fo lowing 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. Fo lowing intraoral administration of a near maximum dose of 476 mg, articaine reaches peak blood concentrations of 2037 and 2145 ng/mL for articaine solution containing 1:100,000 and 1:200,000 epinephrine, respectively, approximately 22 minutes post-dose.

Distribution: Approximately 60 to 80% of articaine HCl is bound to human serum albumin and α-globulins at 37°C *in vitro*.

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

Excretion: At the dose of 476 mg of articaine, the elimination half-l fe was 43.8 minutes and 44.4 minutes for articaine solution containing 1:100,000 and 1:200,000 epinephrine, respectively. Articaine is excreted primarily through urine with 53 - 57% of the administered dose eliminated in the first 24 hours fo lowing 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 ZORCAINE with epinephrine 1:100,000 injection or articaine hydrochloride 4% with epinephrine 1:200,000 injection in pediatric subjects.

Race: There is insufficient information to determine whether the pharmacokinetics of ZORCAINE with epinephrine 1:100,000 injection or articaine hydrochloride 4% with epinephrine 1:200,000 injection differs by race.

Renal and Hepatic Insufficiency: No studies have been performed with ZORCAINE with epinephrine 1:100,000 injection or articaine hydrochloride 4% w th epinephrine 1:200,000 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 ZORCAINE with epinephrine 1:100,000 or articaine hydrochloride 4% with epinephrine 1:200,000 has been shown to be within 1 to 9 minutes of injection. Complete anesthesia lasts approximately 1 hour for infi trations and up to approximately 2 hours for nerve block.

Administration of articaine HCl with epinephrine results in a 3- to 5-fold increase in plasma epinephrine concentrations compared to baseline; however, in hea thy 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 ZORCAINE with epinephrine 1:100,000 as a dental anesthetic. Patients ranging in age from 4 years to over 65 years old underwent simple dental procedures such as single uncomp icated 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. ZORCAINE with epinephrine 1:100,000 was administered as submucosal infiltration and/or nerve block. Efficacy was measured 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.

Four randomized, double blind, active-controlled studies were performed comparing ZORCAINE with epinephrine 1:100,000 versus articaine hydrochloride 4% with epinephrine 1:200,000. The first two studies used electric pulp testers (EPT) to evaluate the success rate (maximum EPT value w thin 10 minutes), onset, and duration of ZORCAINE with epinephrine 1:100,000 versus articaine hydrochloride 4% with epinephrine 1:200,000 as well as articaine solution without epinephrine in healthy adults between 18 and 65 years old. Results indicated that the anesthetic characteristics of the 1:100,000 and 1:200,000 formulations are not significantly different. A third study compared the difference in visualization of the surgical field after administration of ZORCAINE with epinephrine 1:100,000 versus articaine hydrochloride 4% with epinephrine 1:200,000 during bilateral maxillary periodontal surgeries in patients ranging from 21 to 65 years old. ZORCAINE w th epinephrine 1:100,000 provided better visualization of the surgical field and less blood loss during the procedures. In a fourth study, when administration of the maximum dose of each formulation was used, no clinically relevant differences in blood pressure or heart rate were observed.

INDICATIONS AND USAGE

ZORCAINE with epinephrine 1:100,000 and articaine hydrochloride 4% w th epinephrine 1:200,000 are indicated for local, infiltrative, or conductive anesthesia in both simple and complex dental procedures. ZORCAINE with epinephrine 1:100,000 is preferred during operative or surgical procedures when improved visualization of the surgical field is desirable.

CONTRAINDICATIONS

ZORCAINE with epinephrine 1:100,000 and articaine hydrochloride 4% with epinephrine 1:200,000 are 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 ZORCAINE with epinephrine 1:100,000 or articaine hydrochloride 4% with epinephrine 1:200,000 are 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.

ZORCAINE with epinephrine 1:100,000 and articaine hydrochloride 4% with epinephrine 1:200,000 contain epinephrine that can cause local tissue necrosis or systemic toxicity. Usual precautions for epinephrine administration should be observed.

ZORCAINE with epinephrine 1:100,000 and articaine hydrochloride 4% with epinephrine 1:200,000 contain sodium metabisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and ife-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sens tivity in the general population is unknown. Sulfite sensitivity is seen more frequently in asthmatic than in non-asthmatic people.

ZORCAINE with epinephrine 1:100,000 and articaine hydrochloride 4% with epinephrine 1:200,000, along with other local anesthetics, are capable of producing methemoglobinemia. The clinical signs of methemoglobinemia are cyanosis of the nail beds and lips, fatigue and weakness. If methemoglobinemia does not respond to administration of oxygen, administration of methylene blue intravenously 1-2 mg/kg body weight over a 5 minute period is recommended.

The American Heart Association has made the following recommendation regarding the use of local anesthetics with vasoconstrictors in patients with ischemic heart disease: "Vasoconstrictor agents should be used in local anesthesia solutions during dental practice only when it is clear that the procedure will be shortened or the analgesia rendered more profound. When a vasoconstrictor is indicated, extreme care should be taken to avoid intravascular injection. The minimum possible amount of vasoconstrictor should be used." (Kaplan, EL, editor: Cardiovascular disease in dental practice, Dallas 1986, American Heart Association.)

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 ZORCAINE with epinephrine 1:100,000 or articaine hydrochloride 4% with epinephrine 1:200,000 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.

ZORCAINE with epinephrine 1:100,000 and articaine hydrochloride 4% with epinephrine 1:200,000 should be used with caution in patients with heart block.

Local anesthetic solutions, such as ZORCAINE w th epinephrine 1:100,000 and articaine hydrochloride 4% with epinephrine 1:200,000, 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. ZORCAINE w th epinephrine 1:100,000 and articaine hydrochloride 4% with epinephrine 1:200,000 should be used with caution in patients during or following the administration of potent general anesthetic agents, since cardiac arrhythmias may occur under such cond tions.

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, contractil ty, and peripheral vascular resistance are minimal. However, toxic blood concentrations depress cardiac conduction and exc tab lity, which may lead to atrioventricular block, ventricular arrhythmias, and cardiac arrest, poss bly resulting in fatal ties. In addition, myocardial contractility is depressed and peripheral vasod lation occurs, leading to decreased cardiac output and arterial blood pressure.

Careful and constant monitoring of cardiovascular and respiratory (adequacy of ventilation) v tal signs and the patient's state of consciousness should be performed 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.

ZORCAINE with epinephrine 1:100,000 and articaine hydrochloride 4% with epinephrine 1:200,000 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.

Zorcaine Instruction Sheet (US-Front)
PN2560_2

(b) (4)

Sma l 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.

Patients should be instructed not to eat or drink until normal sensation returns.

Clinically Significant Drug Interactions: The administration of local anesthetic solutions containing epinephrine to patients receiving monoamine oxidase inh b tors, nonselective beta adrenergic antagonists or tricyclic antidepressants may produce severe, prolonged hypertension. Phenothiazines and butyrophenones may reduce or reverse the pressor effect of epinephrine. Concurrent use of these agents should generally be avoided. In s tuations 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 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 rats for ZORCAINE with epinephrine 1:100,000 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 toxic ties were observed when ZORCAINE with epinephrine 1:100,000 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 rabb ts, 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 maternal 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 maternal 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 sim lar study using ZORCAINE with epinephrine 1:100,000 (articaine hydrochloride with epinephrine 1:100,000) rather than articaine hydrochloride alone produced maternal toxicity, but no effects on offspring.

There are no adequate and well-controlled studies in pregnant women. Animal reproduction studies are not always predictive of human response. ZORCAINE with epinephrine 1:100,000 and articaine hydrochloride 4% with epinephrine 1:200,000 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 ZORCAINE with epinephrine 1:100,000 or articaine hydrochloride 4% with epinephrine 1:200,000 is administered to a nursing woman.

Pediatric Use: In c inical trials, 61 pediatric patients between the ages of 4 and 16 years received ZORCAINE with epinephrine 1:100,000. 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 ZORCAINE with epinephrine 1:100,000 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 w th age, body weight, and physical condition. See **DOSAGE AND ADMINISTRATIÓN**.

Geriatric Use: In clinical trials, 54 patients between the ages of 65 and 75 years, and 11 patients 75 years and over received ZORCAINE with epinephrine 1:100,000. Among a l 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 safely 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 ident fied 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 none 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 ZORCAINE with epinephrine 1:100,000 and articaine hydrochloride 4% with epinephrine 1:200,000 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), injection technique, volume of injection, hypersensitivity, or may be idiosyncratic.

The reported adverse events are derived from clinical trials in the US and UK. Table 1 displays the adverse events reported in clinical trials where 882 individuals were exposed to ZORCAINE with epinephrine 1:100,000 and Table 2 displays the adverse events reported in c inical trials where 182 individuals were exposed to ZORCAINE with epinephrine 1:100,000 and 179 individuals were exposed to articaine hydrochloride 4% with epinephrine 1:200,000.

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 c inically relevant.

Body as a Whole: abdominal pain, accidental injury, asthenia, back pain, injection site pain, burning sensation above injection site, malaise, neck pain.

Cardiovascular System: hemorrhage, migraine, syncope, tachycardia, elevated blood pressure.

Digestive System: constipation, diarrhea, dyspepsia, glossitis, gum hemorrhage, mouth ulceration, nausea, stomat tis, tongue edemas, tooth disorder, vomiting.

Hemic and Lymphatic System: ecchymosis, lymphadenopathy.

Metabolic and Nutritional System: edema, thirst.

Musculoskeletal System: arthralgia, myalgia, osteomyel tis.

Nervous System: dizziness, dry mouth, facial paralysis, hyperesthesia, increased salivation, nervousness, neuropathy, paresthesia, somnolence, exacerbation of Kearns-Sayre Syndrome.

Respiratory System: pharyng tis, rhinitis, sinus pain, sinus congestion.

Skin and Appendages: pruritus, skin disorder.

Special Senses: ear pain, taste perversion.

Urogenital System: dysmenorrhea.

Persistent paresthesias of the lips, tongue, and oral tissues have been reported with use of articaine hydrochloride, with slow, incomplete, or no recovery. These post-marketing events have been reported chiefly following nerve blocks in the mandible and have involved the trigeminal nerve and its branches.

Table 1. Adverse Events in controlled trials with an incidence of 1% or greater in patients administered ZORCAINE with epinephrine 1:100,000.

Body system	Zorcaine™ with epinephrine 1:100,000 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%)

Table 2. Adverse Events in controlled trials with an incidence of 1% or greater in patients administered ZORCAINE with epinephrine 1:100,000 and articaine hydrochloride 4% with epinephrine 1:200,000.

Number of patients exposed to drug	Zorcaine™ with epinephrine 1:100,000 (N=182)	Articaine hydrochloride 4% with epinephrine 1:200,000 (N=179)
Number of patients that reported any Adverse Event	35	33
Pain	14 (7.6%)	11 (6.1%)
Headache	6 (3.2%)	9 (5.0%)
Positive blood aspiration into syringe	6 (3.2%)	3 (1.6%)
Swelling	5 (2.7%)	3 (1.6%)
Trismus	3 (1.6%)	1 (0.5%)
Nausea and emesis	0 (0%)	3 (1.6%)
Sleepiness	1 (0.5%)	2 (1.1%)
Numbness and tingling	2 (1.0%)	1 (0.5%)
Palpitation	2 (1.0%)	0 (0%)
Ear symptoms (earache, otitis media)	2 (1.0%)	1 (0.5%)
Cough, persistent cough	2 (1.0%)	0 (0%)

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 patient 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 ZORCAINE with epinephrine 1:100,000 and articaine hydrochloride 4% with epinephrine 1:200,000 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.

For most routine dental procedures articaine hydrochloride 4% w th epinephrine 1:200,000 is preferred. However, when more pronounced hemostasis is required, ZORCAINE with epinephrine 1:100,000 may be used.

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/ b (0.0795 mL/ b) of body weight, e.g. 7 cartridges (11.9 mL) for a 150lb. patient.

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. 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 application of one of the standard pediatric drug formulas. In any case, the maximum dose of 4% articaine HCl should not exceed the equivalent of 7 mg/kg (0.175 mL/kg) or 3.2 mg/lb (0.0795 mL/ b) of body weight.

Table 3. Recommended Dosages

PROCEDURE	Zorcaine™ with epinephrine 1:100,000 and Articaine hydrochloride 4% with epinephrine 1:200,000 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.		

STERILIZATION, STORAGE, AND TECHNICAL PROCEDURES

For chemical disinfection of the carpule, e ther 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 perm t.

HOW SUPPLIED

ZORCAINE with epinephrine 1:100,000 (articaine HCl 4% with epinephrine 1:100,000 injection) and articaine hydrochloride 4% with epinephrine 1:200,000 are available in 1.7 mL glass cartridges, in boxes of 50 cartridges. The products are formulated with a 15% overage of epinephrine.

Store at contro led room temperature, below 25°C (77°F) with brief excursions perm tted between 15° and 30°C (59°F-86°F) (see USP controlled room temperature). Protect from light. DO NOT PERMIT TO FREEZE.

ZORCAINE with epinephrine 1:100,000 is manufactured for:

Cook-Waite

EASTMAN KODAK COMPANY by
Novocol Pharmaceuticals of Canada, Inc.
Cambridge, Ontario, Canada N1R 6X3

Rev. 02/07 (2560-2)

Cook-Waite is a trademark of Eastman Kodak Company.

020725602

Zorcaine Instruction Sheet (US-Back)
PN2560_2

(b) (4)

Cook-Waite

Zorcaine™
with epinephrine 1:100,000
(articaine hydrochloride 4% with epinephrine 1:100,000 injection)

FOR INFILTRATION AND NERVE BLOCK ANESTHESIA

"Rx only"

50 Cartridges: 1.7 mL each

NDC 58472-830-50

"Rx only"

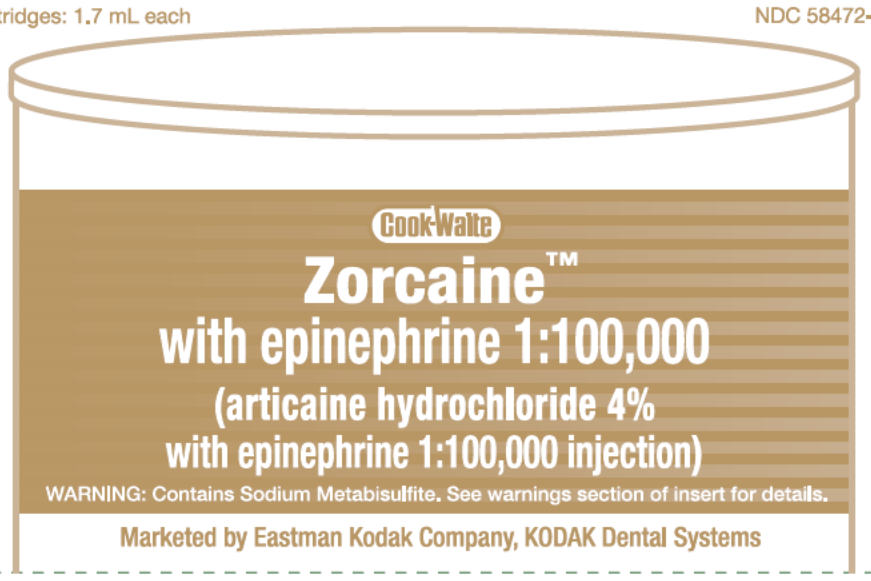
FOR PROFESSIONAL USE ONLY
IN THE PRACTICE OF DENTISTRY

INDICATIONS: This drug product is indicated for local, infiltrative, or conductive anesthesia in both simple and complex dental procedures.

Do not inject intravenously.

Do not use if color is pinkish or darker than slightly yellow or if it contains a precipitate.

CAT 894 2831



Cook-Waite

Zorcaine™
with epinephrine 1:100,000
(articaine hydrochloride 4% with epinephrine 1:100,000 injection)

WARNING: Contains Sodium Metabisulfite. See warnings section of insert for details.

Marketed by Eastman Kodak Company, KODAK Dental Systems

"Rx only"

LOT NO.

EXP.

FOR PROFESSIONAL USE ONLY
IN THE PRACTICE OF DENTISTRY

Keep in carton until ready to use.
DIRECTIONS FOR USE Please consult the insert inside the package.
Store at 25°C (77°F).
WARNING Do not permit to freeze.
Protect from light.
To be sold only as an unbroken package.

MADE IN CANADA

CAT 894 2831

For more information, call 1-800-933-8031 (U.S)
1-800-GO KODAK (Canada) • 1-585-724-5631 (Worldwide)

Manufactured for Eastman Kodak Company by Novocol Pharmaceutical of Canada, Inc.
Cambridge, Ontario, Canada N1R 6X3

(01)50358472830508

+H49189428314P

2123-3

NO INK/
NO COATING

Zorcaine™
with epinephrine 1:100,000
(articaine hydrochloride 4% with epinephrine 1:100,000 injection)

Contents:	Per mL	
Articaine hydrochloride	40	mg
Epinephrine tartrate	0.018	mg
Corresponding in epinephrine base to	0.01	mg
Sodium chloride	1.60	mg
Sodium metabisulfite	0.50	mg
Sodium hydroxide q.s. to adjust pH		
Water for injection, q.s. ad	1	mL

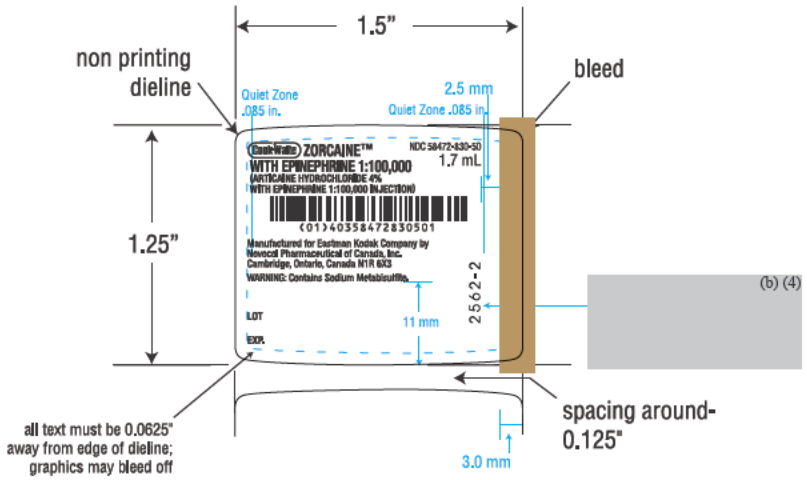
NO INK/
NO COATING

Zorcaine Carton T.S. (US)
CAT 894 2831
ITEM NO. 2123-3/02/07

(b) (4)

LW 02.26.07

*PANTONE is a trademark of Pantone, Inc.
**Refer to current PANTONE Color Publications for the accurate color.



Zorcaine (U.S.)
1.7 ml Label

(b) (4)

LW 07.12.06

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-971/S009

MEDICAL REVIEW(S)

FDA CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS
HFD-170, Room 9B-45, 5600 Fishers Lane, Rockville MD 20857
Tel: (301) 827-7412, FAX: (301) 443-7068

Medical Officer Review

NDA: 20-971 Septocaine™ (Articaine Hydrochloride/Epinephrine Injection) 4%/1:100,000
Review Date: January 31, 2005
Drug Name: Zorcaine, (Articaine Hydrochloride/Epinephrine Injection) 4%/1:100,000
Sponsor: Deproco, Inc.
Type of Submission: Labeling Supplement 009
Date of Submission: August 4, 2004
Date of Receipt: August 5, 2004
Reviewer: Lex Schultheis, M.D., Ph.D.
Project Manager: Allison Meyer

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, Zorcaine 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

(b) (4) 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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-971/S009

OTHER REVIEW(S)

Division of Anesthetic, Critical Care, and Addiction Drug Products

REGULATORY PROJECT MANAGER REVIEW

Application Number: N20-971/S-009

Name of Drug: Septocaine® (Articaine Hydrochloride 4% (40 mg/mL0 with Epinephrine 1:100,000 Injection)

Applicant: Deproco, Inc

Material Reviewed:

Submission Date(s): August 4, 2004

Receipt Date(s): August 5, 2004

Reviewed By: Allison Meyer, Regulatory Project Manager

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 Manger

Supervisory Comment/Concurrence:

Parinda Jani
Chief, Project Management Staff

Drafted: AJM/January 19, 2005
Revised/Initialed:
Finalized:
Filename: Document2

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/

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)

DATE RECEIVED: Aug. 20, 2004	**DESIRED COMPLETION DATE:** October 20, 2004 **PDUFA DATE:** February 1, 2005	**ODS CONSULT #:** 04-0238

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 **NDA #: 20-971/S-009**	**SPONSOR:** Deproco, Inc.

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

Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-420; Parklawn Rm. 6-34
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

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,ii] as well as several FDA databases[iii] 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

[i] MICROMEDEX Integrated Index, 2004, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.
[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[iv] and the data provided by Thomson & Thomson's SAEGIS™ Online Service[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).

[iv] WWW location http://www.uspto.gov.

[v] Data provided by Thomson & Thomson's SAEGIS(tm) Online Service, available at www.thomson-thomson.com.

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

<table>
<tr><th>Product Name</th><th>Dosage form(s), Established name</th><th>Usual adult Dose*</th><th>Other **</th></tr>
<tr><td>Zorcaine (Rx)</td><td>Articaine/Epinephrine Injection 4%/1:100,000</td><td>
<table>
<tr><th>PROCEDURE</th><th colspan="2">Zorcaine™ Injection</th></tr>
<tr><td></td><td>Vol (mL)</td><td>Total Dose of Articaine (HCl) (mg)</td></tr>
<tr><td>Infiltration</td><td>0.5-2.5</td><td>20-100</td></tr>
<tr><td>Nerve block</td><td>0.5-3.4</td><td>20-136</td></tr>
<tr><td>Oral surgery</td><td>1.0-5.1</td><td>40-204</td></tr>
<tr><td colspan="3">THE ABOVE SUGGESTED VOLUMES SERVE ONLY AS A GUIDE. OTHER VOLUMES MAY BE USED PROVIDED THE TOTAL MAXIMUM RECOMMENDED DOSE IS NOT EXCEEDED.</td></tr>
</table>
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><td></td></tr>
<tr><td>Marcaine (Rx)

and

Sensorcaine (Rx)</td><td>Bupivicaine Injection 0.25%, 0.5%, 0.75%

Bupivicaine/Epinephrine 0.25%/1:200,000, 0.5%/1:200,000, 0.75%/1:200,000, and 0.75%/1:200,000</td><td>
Bupivacaine Recommended Concentrations and Doses
<table>
<tr><th>Type of block</th><th>Concentration</th><th colspan="2">Each dose</th><th>Motor block[1]</th></tr>
<tr><td></td><td></td><td>(mL)</td><td>(mg)</td><td></td></tr>
<tr><td>Local infiltration</td><td>0.25%[2]</td><td>max</td><td>Max</td><td>--</td></tr>
<tr><td>Epidural</td><td>0.75%[2,3]</td><td>10-20</td><td>75-150</td><td>complete</td></tr>
<tr><td></td><td>0.5%[2]</td><td>10-20</td><td>50-100</td><td>moderate to complete</td></tr>
<tr><td></td><td>0.25%[2]</td><td>10-20</td><td>25-50</td><td>partial to moderate</td></tr>
<tr><td>Caudal</td><td>0.5%[2]</td><td>15-30</td><td>75-150</td><td>moderate to complete</td></tr>
<tr><td></td><td>0.25%[2]</td><td>15-30</td><td>37.5-75</td><td>moderate</td></tr>
<tr><td>Peripheral nerves</td><td>0.5%[2]</td><td>5 - max.</td><td>25-max.</td><td>moderate to complete</td></tr>
<tr><td></td><td>0.25%[2]</td><td>5 max.</td><td>12.5-max.</td><td>moderate to complete</td></tr>
<tr><td>Retrobulbar</td><td>0.75%[2]</td><td>2- 4</td><td>15-30</td><td>complete</td></tr>
<tr><td>Sympathetic</td><td>0.25%</td><td>20-50</td><td>50-125</td><td>--</td></tr>
<tr><td>Epidural test dose</td><td>0.5% w/epi</td><td>2-3</td><td>10-15 (10-15 mcg epi)</td><td>--</td></tr>
</table>
</td><td>**L/A, S/A

**S/A</td></tr>
<tr><td>Novocaine (Rx)</td><td>Procaine Injection 1%, 2%, and 10%</td><td>
<u>Infiltration anesthesia:</u>
350 mg to 600 mg of a 0.25% to 0.5% solution.
<u>Peripheral nerve block</u>
Up to 200 mL of 0.5% solution or up to 50 mL of a 2% solution.
<u>Spinal anesthesia</u>
Recommended Procaine Dosage for Spinal Anesthesia
<table>
<tr><th>Extent of anesthesia</th><th colspan="2">Procaine 10%solution</th><th>Total dose (mg)</th><th>Site of injection (lumbar interspace)</th></tr>
<tr><td></td><td>Volume of 10% solution (mL)</td><td>Volume of diluent (mL)</td><td></td><td></td></tr>
<tr><td>Perineum</td><td>0.5</td><td>0.5</td><td>50</td><td>4th</td></tr>
<tr><td>Perineum and lower extremities</td><td>1</td><td>1</td><td>100</td><td>3rd or 4th</td></tr>
<tr><td>Up to costal margin</td><td>2</td><td>1</td><td>200</td><td>2nd, 3rd, or 4th</td></tr>
</table>
</td><td>**L/A, S/A</td></tr>
<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><td>**L/A</td></tr>
<tr><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><td>**S/A</td></tr>
<tr><td>Zocor (Rx)</td><td>Simvistatin 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><td>**L/A</td></tr>
</table>

<table>
<tr><th>Product Name</th><th>Dosage form(s), Established name</th><th>Usual adult Dose*</th><th>Other **</th></tr>
<tr><td>Zorcaine (Rx)</td><td>Articaine/Epinephrine Injection 4%/1:100,000</td><td>
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<tr><td colspan="3">THE ABOVE SUGGESTED VOLUMES SERVE ONLY AS A GUIDE. OTHER VOLUMES MAY BE USED PROVIDED THE TOTAL MAXIMUM RECOMMENDED DOSE IS NOT EXCEEDED.</td></tr>
</table>
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><td></td></tr>
<tr><td>Psorcon (Rx)

Psorcon-E (Rx)</td><td>Diflorasone Ointment 0.05%

Diflorasone Emollient Cream 0.05%</td><td>Apply a thin film 1 to 3 times daily.

Apply a thin film 1 to 3 times daily.</td><td>**S/A</td></tr>
<tr><td>Septocaine (Rx)</td><td>Articaine/Epinephrine Injection 4%/1:100,000</td><td>
<table>
<tr><th colspan="3">Articaine HCl Recommended Dosages[1]</th></tr>
<tr><td>Procedure</td><td>Volume (mL)</td><td>Total dose of articaine HCl(mg)</td></tr>
<tr><td>Infiltration</td><td>0.5 to 2.5</td><td>20 to 100</td></tr>
<tr><td>Nerve block</td><td>0.5 to 3.4</td><td>20 to 136</td></tr>
<tr><td>Oral surgery</td><td>1 to 5.1</td><td>40 to 204</td></tr>
</table>
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><td>**S/A</td></tr>
<tr><td colspan="4">*Frequently used, not all-inclusive.
**L/A (look-alike), S/A (sound-alike)</td></tr>
</table>

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 though 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 Zorcaine were discussed by the Expert Panel (EPD).

C. AERS AND DQRS DATABASE RESEARCH

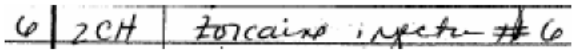
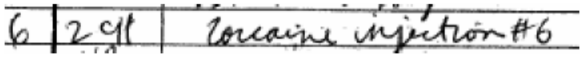
DMETS searched *the* FDA Adverse Event Reporting System *(AERS)* and the Drug Quality Reporting System *(DQRS)* database in order to identify any post-marketing safety cases of medication errors associated with products ending with the "caine'. AERS was searched for domestic cases using the MedDRA Preferred Terms of "Medication Error", "Overdose", "Accidental Overdose," "Pharmaceutical Product Complaint," and drug names of Septocaine, Marcaine, Sensorcaine, Novocaine, Soriatane, Bupivicaine, Procaine, 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 (bupivicaine) 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.

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Pharmacy Requisition: 	Zorcaine Injection, #6, order code ZCH.
Pharmacy Requisition: 	

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.

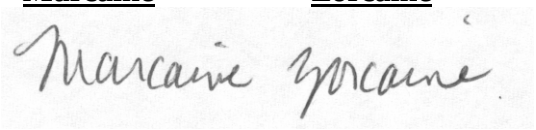
E. SAFETY EVALUATOR RISK ASSESSMENT

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 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 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.

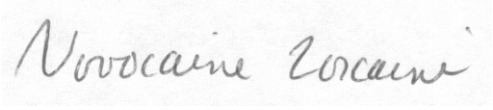
Marcaine **Zorcaine**



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 "sorcaine" 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, where as 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 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, where as 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.

Novocaine **Zorcaine**



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 RLEATED 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

1. See comments A-1 and A-2.

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 LABEING

Delete trailing zeros appearing in the table in the DOSAGE AND ADMINSITRATION 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

Pharmacy Requisition #1	**Pharmacy Requisition 2**	**Voicemail**
Torcaine injection	Lorcaine	Lorepen Inj
Zocaine	Lorcaine	Lortane
Zorcaine	Lorcaine injection	Lortane
Zorcaine	Lorcaine injection	Lortane
Zorcaine	Zorcaine	Lortane Injection
Zorcaine	Zorcaine	Lortane Injection
Zorcaine	Zorcaine	Zorbine Injection
Zorcaine	Zorcaine	Zorcane Injection
Zorcaine	Zorcaine	Zorotene injection
Zorcaine	Zorcaine	Zorpain inj
Zorcaine Injection	Zorcaine In	
Zorcaine injection	Zorcaine Inj	
Zorcaine injection	Zorcaine injection	
Zorcaine injection	Zorcaine injection	
Zorcaine injection	Zorcaine injection	
Zorcaine injection	Zorcaine injection	
Zorcaine Injection	Zorcaine injection	
Zortain Injection	Zorcaine Injection	
	Zorcaine injection	
	Zorcaine	

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/s/

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-971/S009

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

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/s/

Allison Meyer
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CSO

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

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 827-7431	METHOD OF DELIVERY (Check one): X MAIL ○ HAND
SIGNATURE OF RECEIVER:	SIGNATURE OF DELIVERER:

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/s/

Allison Meyer
8/24/04 08:57:51 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

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

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/s/

Allison Meyer
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