CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

20-971/S013

Trade Name: Septocaine®

Generic Name: articaine hydrochloride; epinephrine bitartrate

Sponsor: Deproco, Inc.

Approval Date: 3/30/2006

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-971/S013

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Reviews / Information Included in this NDA Review.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-971/S013

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-010

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

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

Dear Mr. Matelski:

Please refer to your new drug application (NDA) dated September 29, 2005, received September 30, 2005, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Tradename (articaine HCl 4% and epinephrine 1:200,000 injection).

We acknowledge receipt of your submissions dated November 1, December 21 and 27, 2005, January 23, February 3, 10, and 21, and March 9, 22, 23, and 29, 2006.

This new drug application provides for the use of Septocaine® (articaine HCl 4% and epinephrine 1:200,000 injection) for infiltration or nerve block anesthesia for dentistry.

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, with the minor editorial revision listed below.

1. You have agreed to remove the (b) (4) symbol from in front of the tradename "Septocaine" on the carton and container labels.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, 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 NDA 22-010**." Approval of this submission by FDA is not required before the labeling is used.

If you choose to use a proprietary name for this product, the name and its use in the labels must conform to the specifications under 21 CFR 201.10 and 201.15. We recommend that you submit any proprietary name to the Agency for our review prior to its implementation.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

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

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81). All 15-day alert reports, periodic (including quarterly) adverse drug experience reports, field alerts, annual reports, supplements, and other submissions should be addressed to the original NDA 20-971 for this drug product, not to this NDA. In the future, do not make submissions to this NDA except for the final printed labeling requested above.

If you have any questions, call Allison Meyer, Regulatory Project Manager, at (301) 796-1258

Sincerely,

{See appended electronic signature page}

Bob A. Rappaport, MD
Director
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

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

/s/

Bob Rappaport

3/30/2006 05:29:09 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-971/S013

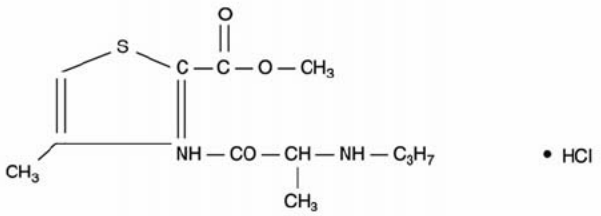
LABELING

Septocaine® with epinephrine 1:100,000
Septocaine® with epinephrine 1:200,000
(articaine hydrochloride 4% (40 mg/mL) with epinephrine 1:100,000 or 1:200,000 injection)

For Infiltration and Nerve Block Anesthesia

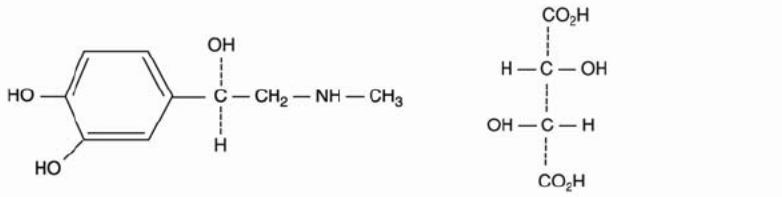
DESCRIPTION

Septocaine® injection is a sterile, aqueous solution that contains articaine HCl 4% (40mg/mL) with epinephrine bitartrate in a 1:100,000 or 1:200,000 strength. Articaine HCl is a local anesthetic, which is chemically designated as 4-methyl-3-[2-(propylamino)-propionamido]-2-thiophene-carboxylic acid, methyl ester hydrochloride and is a racemic mixture. Articaine HCl has a molecular weight of 320.84 and the molecular and structural formulae are displayed below:



$C_{13}H_{20}N_2O_3S \cdot HCl$

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:



$C_9H_{13}NO_3 \cdot C_4H_6O_6$

Septocaine® contains articaine HCl (40mg/mL), epinephrine as bitartrate (1:100,000 or 1:200,000), sodium chloride (1.6 mg/mL), and sodium metabisulfite (0.5 mg/mL). The product is formulated with a 15% overage of epinephrine. The pH is adjusted with sodium hydroxide.

CLINICAL PHARMACOLOGY

PHARMACOKINETICS

Absorption: Following dental injection by the submucosal route of an articaine solution containing 1:200,000 epinephrine, articaine reaches peak blood concentration about 25 minutes after a single dose injection and 48 minutes after three doses. Peak plasma levels of articaine achieved after 68 and 204 mg doses are 385 and 900 ng/mL, respectively. Following 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 γ-globulins at 37°C *in vitro*.

Metabolism: Articaine HCl is rapidly metabolized by plasma carboxyesterase to its primary metabolite, articainic acid, which is inactive. *In vitro* studies show that the human liver 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-life 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 following submucosal administration. Articainic acid is the primary metabolite in urine. A minor metabolite, articainic acid glucuronide, is also excreted in urine. Articaine constitutes only 2% of the total dose excreted in urine.

SPECIAL POPULATIONS

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

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

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

PHARMACODYNAMICS

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

The onset of anesthesia, following administration of Septocaine has been shown to be within 1 to 9 minutes of injection. Complete anesthesia lasts approximately 1 hour for infiltrations 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 healthy adults it does not appear to be associated with marked increases in blood pressure or heart rate, except in the case of accidental intravascular injection (see WARNINGS).

CLINICAL TRIALS

Three randomized, double-blind, active-controlled studies were designed to evaluate effectiveness of Septocaine® with epinephrine 1:100,000 as a dental anesthetic. Patients ranging in age from 4 years to over 65 years old Septocaine underwent simple dental procedures such as single uncomplicated extractions, routine operative procedures, single apical resections, and single crown procedures, and complex dental procedures such as multiple extractions, multiple crowns and/or bridge procedures, multiple apical resections, alveolectomies, muco-gingival operations, and other surgical procedures on the bone. Septocaine® 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 Septocaine® with epinephrine 1:100,000 versus Septocaine with epinephrine 1:200,000. The first two studies used electric pulp testers (EPT) to evaluate the success rate (maximum EPT value within 10 minutes), onset, and duration of Septocaine® with epinephrine 1:100,000 versus Septocaine 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 Septocaine® with epinephrine 1:100,000 versus Septocaine with epinephrine 1:200,000 during bilateral maxillary periodontal surgeries in patients ranging from 21 to 65 years old. Septocaine® with 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

Septocaine® is indicated for local, infiltrative, or conductive anesthesia in both simple and complex dental procedures. Septocaine® with epinephrine 1:100,000 is preferred during operative or surgical procedures when improved visualization of the surgical field is desirable.

CONTRAINDICATIONS

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

WARNINGS

Accidental intravascular injection may be associated with convulsions, followed by central nervous system or cardiorespiratory depression and coma, progressing ultimately to respiratory arrest. Dental practitioners and/or clinicians who employ local anesthetic agents should be well versed in diagnosis and management of emergencies that may arise from their use. Resuscitative equipment, oxygen, and other resuscitative drugs should be available for immediate use.

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

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

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

Septocaine®, 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 Septocaine® may cause significant increases in blood levels with each repeated dose because of possible accumulation of the drug or its metabolites. Tolerance to elevated blood levels varies with the status of the patient.

Debilitated patients, elderly patients, acutely ill patients and pediatric patients should be given reduced doses commensurate with their age and physical condition.

Septocaine® should be used with caution in patients with heart block.

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

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

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

Septocaine® should also be used with caution in patients with impaired cardiovascular function since they may be less able to compensate for functional changes associated with the prolongation of A-V conduction produced by these drugs.

Small doses of local anesthetics injected in dental blocks may produce adverse reactions similar to systemic toxicity seen with unintentional intravascular injections of larger doses. Confusion, convulsions, respiratory depression and/or respiratory arrest, and cardiovascular stimulation or depression have been reported. These reactions may be due to intra-arterial injection of the local anesthetic with retrograde flow to the cerebral circulation. Patients receiving these blocks should be observed constantly. Resuscitative equipment and personnel for treating adverse reactions should be immediately available.

Dosage recommendations should not be exceeded (see DOSAGE and ADMINISTRATION).

Information for Patients:

- The patient should be informed in advance of the possibility of temporary loss of sensation and muscle function following infiltration and nerve block injections.
- 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 inhibitors, nonselective beta andregernic 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 situations when concurrent therapy is necessary, careful patient monitoring is essential.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Studies to evaluate the carcinogenic potential of articaine HCl in animals have not been conducted. Five standard mutagenicity tests, including three *in vitro* tests (the nonmammalian Ames test, the mammalian Chinese hamster ovary chromosomal aberration test and a mammalian gene mutation test with articaine HCl) and two *in vivo* mouse micronucleous tests (one with Septocaine® 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 Septocaine® 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 toxicities were observed when Septocaine® 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 rabbits, 80 mg/kg (approximately 4 times the maximum recommended human dose on a mg/m^2 basis) did cause fetal death and increase fetal skeletal variations, but these effects may be attributable to the severe 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 similar study using Septocaine® with epinephrine 1:100,000 (articaine hydrochloride and 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. Septocaine® with epinephrine 1:100,000 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 Septocaine® with epinephrine 1:100,000 is administered to a nursing woman.

Pediatric Use: In clinical trials, 61 pediatric patients between the ages of 4 and 16 years received Septocaine® 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 Septocaine® 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 with age, body weight, and physical condition. See DOSAGE AND ADMINISTRATION.

Geriatric Use: In clinical trials, 54 patients between the ages of 65 and 75 years, and 11 patients 75 years and over received Septocaine® with epinephrine 1:100,000. Among all patients between 65 and 75 years, doses from 0.43 mg/kg to 4.76 mg/kg (0.9 to 11.9 mL) were administered safely to 35 patients for simple procedures and doses from 1.05 mg/kg to 4.27 mg/kg (1.3 to 6.8 mL) were administered safely to 19 patients for complex procedures. Among the 11 patients ≥ 75 years old, doses from 0.78 mg/kg to 4.76 mg/kg (1.3 to 11.9 mL) were

administered safely to 7 patients for simple procedures and doses of 1.12 mg/kg to 2.17 mg/kg (1.3 to 5.1 mL) were 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 identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Approximately 6% of patients between the ages of 65 and 75 years and 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 Septocaine® are characteristic of those associated with other amide-type local anesthetics. Adverse reactions to this group of drugs may also result from excessive plasma levels (which may be due to overdosage, unintentional intravascular injection, or slow metabolic degradation), 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 Septocaine® with epinephrine 1:100,000 and Table 2 displays the adverse events reported in clinical trials where 182 individuals were exposed to Septocaine® with epinephrine 1:100,000 and 179 individuals were exposed to Septocaine® with epinephrine 1:200,000.

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

Body System	**Septocaine® 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 Septocaine® (articaine hydrochloride 4% (40 mg/mL) with epinephrine 1:100,000 Injection) and (articaine hydrochloride 4% (40 mg/mL) with epinephrine 1:200,000 Injection).

Number of patients exposed to drug	Septocaine® with epinephrine 1:100,000 (N= 182)	Septocaine® 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%)

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

Body as a Whole: abdominal pain, accidental injury, asthenia, back pain, injection site pain, 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, stomatitis, tongue edemas, tooth disorder, vomiting.

Hemic and Lymphatic System: ecchymosis, lymphadenopathy.

Metabolic and Nutritional System: edema, thirst.

Musculoskeletal System: arthralgia, myalgia, osteomyelitis.

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

Respiratory System: pharyngitis, 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.

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

For most routine dental procedures Trade Name is preferred. However, when more pronounced hemostasis is required, Septocaine® may be used.

Table 2. Recommended Dosages

Procedure	**Septocaine® Injection**	
	Volume (mL)	**Total dose of articaine HCl (mg)**
Infiltration	0.5 – 2.5	20 – 100
Nerve block	0.5 – 3.4	20 – 136
Oral surgery	1.0 – 5.1	40 – 204
The above suggested volumes serve only as a guide. Other volumes may be used provided the total maximum recommended dose is not exceeded.		

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

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

MAXIMUM RECOMMENDED DOSAGES

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

STERILIZATION, STORAGE, AND TECHNICAL PROCEDURES

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

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

HOW SUPPLIED
Septocaine® (articaine HCl 4% with epinephrine 1:100,000 or 1:200,000 injection) is available in 1.7 mL glass cartridges, in boxes of 50 cartridges. The product is formulated with a 15% overage of epinephrine.

NDC 51004-1050-2 Septocaine® with epinephrine 1:100,000 Box of 50 cartridges
NDC 51004-1049-2 Septocaine® with epinephrine 1:200,000 Box of 50 cartridges

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.

Manufactured in Canada by: Novocol Pharmaceutical of Canada, Inc.

Distributed by: SEPTODONT, Inc.,
245, Quigley Boulevard-Suite C
New Castle, Delaware 19720-4105

Rev. 09/05 (2552-X)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-971/S013

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-971/S-013 **CBE-0 SUPPLEMENT**

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

Attention: Wayne Matelski, Esquire
Counsel to and Official Correspondent 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
NDA Number:	20-971
Supplement number:	013
Date of supplement:	October 7, 2005
Date of receipt:	October 11, 2005

This supplemental application, submitted as [redacted] (b) (4)

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on December 12, 2005 in accordance with 21 CFR 314.101(a).

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

Sincerely,

{See appended electronic signature page}

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

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

/s/

Allison Meyer

10/20/2005 11:47:10 AM