CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

20971/S021

Trade Name:	Septocaine® (articaine HCl and epinephrine) Injection
Generic Name:	articaine hydrochloride 4% and epinephrine 1:200,000 injection; articaine hydrochloride 4% and epinephrine 1:100,000 injection
Sponsor:	Deproco, Inc.
Approval Date:	02/22/2010
Indication:	For local, infiltrative, or conductive anesthesia in both simple and complex dental procedures.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20971/S021

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 020971/S-021 **SUPPLEMENT APPROVAL**

Deproco, Inc.
c/o Arent Fox LLP
1050 Connecticut Ave, NW
Washington, DC 20036-5339

Attention: Wayne H. Matelski
Official Correspondent and Counsel

Dear Mr. Matelski:

Please refer to your supplemental new drug application dated June 29, 2009, received June 30, 2009, submitted under section 505(b)of the Federal Food, Drug, and Cosmetic Act (FDCA) for Septocaine® (articaine hydrochloride 4% and epinephrine 1:100,000 and 1:200,000) Injection.

We acknowledge receipt of your submission dated January 29, 2010.

This prior approval supplemental new drug application proposes conversion of the content of the currently approved package insert into the Physicians Labeling Rule (PLR) format as set forth under 21 CFR 201.56 and 21 CFR 201.57.

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 enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical to the enclosed labeling text for the package insert. For administrative purposes, please designate this submission, "SPL for approved NDA 20971/S-021."

PROMOTIONAL MATERIALS

All promotional materials for your drug product that include representations about your drug product must be promptly revised to make it consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions to your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the following address or by facsimile at 301-847-8444:

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

In addition, as required under 21 CFR 314.81(b)(3)(i), you must submit your updated final promotional materials, and the package insert at the time of initial dissemination or publication, accompanied by a Form FDA-2253, directly to the above address. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

LETTERS TO HEALTH CARE PROFESSIONALS

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

MedWatch
Food and Drug Administration
5600 Fishers Lane, Room 12B05
Rockville, MD 20857

REPORTING REQUIREMENTS

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 Kimberly Compton, Regulatory Project Manager, at (301) 796-1191.

Sincerely,

{See appended electronic signature page}

Bob A. Rappaport, M.D.
Director
Division of Anesthesia, Analgesia and
Rheumatology Drugs
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure- Content of Labeling

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20971	SUPPL-21	DEPROCO INC	SEPTOCAINE

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

/s/

LARISSA LAPTEVA
02/22/2010
for Bob Rappaport, M.D.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20971/S021

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use Septocaine® safely and effectively. See full prescribing information for Septocaine®.

Septocaine® (articaine HCl and epinephrine) Injection; Intraoral Submucosal Injection

Articaine hydrochloride 4% and epinephrine 1:200,000

Articaine hydrochloride 4% and epinephrine 1:100,000

Initial U.S. Approval: 2000

----------INDICATIONS AND USAGE----------
Septocaine®, an amide local anesthetic containing a vasoconstrictor, is indicated for local, infiltrative, or conductive anesthesia in both simple and complex dental procedures.

----------DOSAGE AND ADMINISTRATION----------
For dental injection by submucosal infiltration or nerve block. (2.1)
- For infiltration: 0.5-2.5 mL (20-100 mg articaine HCl) (2.1)
- For nerve block: 0.5-3.4 mL (20-136 mg articaine HCl) (2.1)
- For oral surgery: 1.0-5.1 mL (40-204 mg articaine HCl) (2.1)
- For most routine dental procedures, Septocaine® containing epinephrine 1:200,000 is preferred. However, when more pronounced hemostasis or improved visualization of the surgical field are required, Septocaine® containing epinephrine 1:100,000 may be used. (2.1)
- Dosages should be reduced in pediatric patients, elderly patients, and patients with cardiac or liver disease. (2.1)

Maximum recommended dosages (2.2):
- Adults: 7 mg/kg (0.175 mL/kg)
- Children 4-16 years: 7 mg/kg (0.175 mL/kg), depending on the age, weight and magnitude of the operation.

----------DOSAGE FORMS AND STRENGTHS----------
Injection (clear colorless solution), containing:
- Articaine hydrochloride 4% (40 mg/mL) and epinephrine 1:200,000 (as epinephrine bitartrate 0.009 mg/mL) (3)
- Articaine hydrochloride 4% (40 mg/mL) and epinephrine 1:100,000 (as epinephrine bitartrate 0.018 mg/mL) (3)

----------CONTRAINDICATIONS----------
Known hypersensitivity to sulfite (4)

----------WARNINGS AND PRECAUTIONS----------
- **Accidental Intravascular Injection:** May be associated with convulsions followed by coma and respiratory arrest. Resuscitative equipment, oxygen and other resuscitative drugs should be available. (5.1)
- **Systemic Toxicity** (5.2)
- **Vasoconstrictor Toxicity:** Local anesthetic solutions like Septocaine® that contain a vasoconstrictor should be used cautiously, especially in patients with impaired cardiovascular function or vascular disease. (5.3)
- **Methemoglobinemia** (5.4)
- **Anaphylaxis and Allergic-Type Reactions** (5.5)

----------ADVERSE REACTIONS----------
The most common adverse reactions (incidence >2%) are headache and pain. (6.1)
To report SUSPECTED ADVERSE REACTIONS, contact Septodont at 1-800-872-8305 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Monoamine oxidase inhibitors, nonselective beta adrenergic antagonists, or tricyclic antidepressants may produce severe, prolonged hypertension (7)
- Phenothiazines and butyrophenones may reduce or reverse the pressor effect of epinephrine (7)

----------USE IN SPECIFIC POPULATIONS----------
- **Pregnancy:** Based on animal studies, may cause fetal harm. (8.1)
- **Nursing Mothers:** Exercise caution when administering to a nursing woman. (8.3)
- **Pediatric Use:** Safety and effectiveness in pediatric patients below the age of 4 years have not been established. (8.4)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 12/2009

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Septocaine®, an amide local anesthetic containing a vasoconstrictor, is indicated for local, infiltrative, or conductive anesthesia in both simple and complex dental procedures.

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Information

Table 1 (below) 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 or nerve block.

Table 1: Recommended Dosages for Both Strengths

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 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.

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 because the incidence of side effects may be dose-related.

For most routine dental procedures, Septocaine® containing epinephrine 1:200,000 is preferred. However, when more pronounced hemostasis or improved visualization of the surgical field are required, Septocaine® containing epinephrine 1:100,000 may be used.

2.2 Maximum Recommended Dosages

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

- **Pediatric Patients Ages 4 to 16 Years:** The quantity of articaine HCl in children ages 4 to 16 years of age to be injected should be determined by the age and weight of the child and the magnitude of the operation. The maximum dose of articaine HCl 4% should not exceed 7 mg/kg (0.175 mL/kg) *[see Use in Specific Populations (8.4)]*.
- Safety and effectiveness of Septocaine® in pediatric patients below the age of 4 years have not been established.

2.3 Dosing in Special Populations

Dose reduction may be required in debilitated patients, acutely ill patients, elderly patients, and pediatric patients commensurate with their age and physical condition. No studies have been performed in patients with renal or liver dysfunction. Caution should be used in patients with severe liver disease. [*see Warnings and Precautions (5.2), Use in Specific Populations (8.4, 8.5, and 8.6)]*

3 DOSAGE FORMS AND STRENGTHS

Injection (clear colorless solution), containing:

- Articaine hydrochloride 4% (40 mg/mL) and epinephrine 1:200,000 (as epinephrine bitartrate 0.009 mg/mL)
- Articaine hydrochloride 4% (40 mg/mL) and epinephrine 1:100,000 (as epinephrine bitartrate 0.018 mg/mL)

4 CONTRAINDICATIONS

Septocaine is contraindicated in patients who are hypersensitive to products containing sulfites. Products containing sulfites may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. Sulfite sensitivity is seen more frequently in asthmatic than in non-asthmatic people *[see Warnings and Precautions (5.5)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Accidental Intravascular Injection

Accidental intravascular injection of Septocaine® may be associated with convulsions, followed by central nervous system or cardiorespiratory depression and coma, progressing ultimately to respiratory arrest. Dental practitioners who employ local anesthetic agents including Septocaine® 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. 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.

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 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 (2.1)]*.

5.2 Systemic Toxicity

This includes toxicity arising from accidental intravascular injection of Septocaine® discussed in Section 5.1, as well as that related to higher systemic concentrations of local anesthetics or epinephrine *[see Warnings and Precautions (5.3)]*. Systemic absorption of local anesthetics including Septocaine® can produce effects on the central nervous and cardiovascular systems.

At blood concentrations achieved with therapeutic doses of Septocaine®, changes in cardiac conduction, excitability, refractoriness, contractility, and peripheral vascular resistance are minimal. However, toxic blood concentrations of Septocaine® can 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 vasodilatation occurs, leading to decreased cardiac output and arterial blood pressure. Septocaine® should also be used with caution in patients with heart block as well as those 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.

Restlessness, anxiety, tinnitus, dizziness, blurred vision, tremors, depression, or drowsiness may be early warning signs of central nervous system toxicity.

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 of Septocaine®. Repeated doses of Septocaine® may cause significant increases in blood levels because of possible accumulation of the drug or its metabolites. The lowest dosage that results in effective anesthesia should be used to decrease the risk of high plasma levels and serious adverse effects. Tolerance to elevated blood levels varies with the status of the patient. Resuscitative equipment, oxygen, and other resuscitative drugs should be available for immediate use. Precautions for epinephrine administration, discussed in Section 5.3, should be observed.

Debilitated patients, elderly patients, acutely ill patients, and pediatric patients should be given reduced doses commensurate with their age and physical condition *[see Dosage and Administration (2.1, 2.3)]*. No studies have been performed in patients with liver dysfunction, and caution should be used in patients with severe hepatic disease.

5.3 Vasoconstrictor Toxicity

Septocaine® contains epinephrine, a vasoconstrictor that can cause local or systemic toxicity and should be used cautiously. Local toxicity may include ischemic injury or necrosis, which may be related to vascular spasm. Septocaine® should be used with caution in patients during and following the administration of potent general anesthetic agents, since cardiac arrhythmias may occur under such conditions. Patients with peripheral vascular disease and those with hypertensive vascular disease may exhibit exaggerated vasoconstrictor response.

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, 1986).

It is essential to aspirate before any injection to avoid administration of the drug into the blood stream.

5.4 Methemoglobinemia

Articaine, like other local anesthetics, can cause methemoglobinemia, particularly in conjunction with methemoglobin-inducing agents. Septocaine® should not be used in patients with congenital or idiopathic methemoglobinemia, or in patients who are receiving treatment with methemoglobin-inducing agents since they are more susceptible to drug-induced methemoglobinemia.

Signs and symptoms of methemoglobinemia may be delayed some hours after exposure. Initial signs and symptoms of methemoglobinemia include slate grey cyanosis seen in buccal mucous membranes, lips, and nail beds. In severe cases, symptoms may include central cyanosis, headache, lethargy, dizziness, fatigue, syncope, dyspnea, CNS depression, seizures, dysrythmia, and shock. Methemoglobinemia should be considered if central cyanosis unresponsive to oxygen therapy occurs, especially if methemoglobin-inducing agents have been used. Calculated oxygen saturation and pulse oximetry are inaccurate in the setting of methemoglobinemia. The diagnosis can be confirmed by an elevated methemoglobin level of at least 10% is present. The development of methemoglobinemia is dose-related.

***Management of methemoglobinemia*:** If methemoglobinemia does not respond to administration of oxygen, clinically significant symptoms of methemoglobinemia should be treated with administration of a slow intravenous injection (over 5 minutes) of methylene blue at a dosage of 1-2 mg/kg body weight.

5.5 Anaphylaxis and Allergic-Type Reactions

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.

6 ADVERSE REACTIONS

Reactions to articaine 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, or hypersensitivity or they may be idiosyncratic.

6.1 Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The reported adverse reactions are derived from clinical trials in the United States and the United Kingdom. Table 2 displays the adverse reactions reported in clinical trials where 882 individuals were exposed to Septocaine® containing epinephrine 1:100,000. Table 3 displays the adverse reactions reported in clinical trials where 182 individuals were exposed to Septocaine® containing epinephrine 1:100,000 and 179 individuals were exposed to Septocaine® containing epinephrine 1:200,000.

Adverse reactions observed in at least 1% of patients

Table 2:
Adverse Reactions in Controlled Trials with an Incidence of 1% or Greater in Patients Administered Septocaine® containing Epinephrine 1:100,000

Body System/Reaction	**Septocaine® containing epinephrine 1:100,000 (N=882) Incidence**
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 3:
Adverse Reactions in Controlled Trials with an Incidence of 1% or Greater in Patients Administered Septocaine® containing Epinephrine 1:200,000 and Septocaine® containing Epinephrine 1:100,000

Reaction	Septocaine® with epinephrine 1:200,000 (N=179) Incidence	Septocaine® with epinephrine 1:100,000 (N=182) Incidence
Any adverse reaction	33 (18%)	35 (19%)
Pain	11 (6 1%)	14 (7.6%)
Headache	9 (5%)	6 (3.2%)
Positive blood aspiration into syringe	3 (1.6%)	6 (3.2%)
Swelling	3 (1.6%)	5 (2.7%)
Trismus	1 (0.5%)	3 (1.6%)
Nausea and emesis	3 (1.6%)	0 (0%)
Sleepiness	2 (1.1%)	1 (0.5%)
Numbness and tingling	1 (0.5%)	2 (1%)
Palpitation	0 (0%)	2 (1.%)
Ear symptoms (earache, otitis media)	1 (0.5%)	2 (1%)
Cough, persistent cough	0 (0%)	2 (1%)

Adverse reactions observed in less than 1% of patients

Table 4:
Adverse Reactions in Controlled Trials with an Incidence of Less than 1% but Considered Clinically Relevant in Patients Administered Septocaine®

Body System	Reactions
Body as a Whole	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	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

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of Septocaine®. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a casual relationship to drug exposure.

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

Hypoesthesia has been reported with use of articaine, especially in pediatric age groups, which is usually reversible. Prolonged numbness can result in soft tissue injuries such as that of the lips and tongue in these age groups.

Ischemic injury and necrosis have been described following use of articaine with epinephrine and have been postulated to be due to vascular spasm of terminal arterial branches.

Paralysis of ocular muscles has been reported, especially after posterior, superior alveolar injections of articaine during dental anesthesia. Symptoms include diplopia, mydriasis, ptosis and difficulty in abduction of the affected eye. These symptoms have been described as developing immediately after injection of the anesthetic solution and persisting one minute to several hours, with generally complete recovery.

7 DRUG INTERACTIONS

The administration of local anesthetic solutions containing epinephrine to patients receiving monoamine oxidase inhibitors, 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 be avoided; however, in situations when concurrent therapy is necessary, careful patient monitoring is essential *[see Warnings and Precautions (5.6)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects - Pregnancy Category C.

There are no adequate and well-controlled studies in pregnant women with Septocaine®. Articaine hydrochloride and epinephrine (1:100,000) has been shown to increase fetal deaths and skeletal variations in rabbits when given in doses approximately 4 times the maximum recommended human dose (MRHD). Septocaine® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In embryo-fetal toxicity studies in rabbits, 80 mg/kg, subcutaneously (approximately 4 times the MRHD based on body surface area) caused fetal death and increased fetal skeletal variations, but these effects may be attributable to severe maternal toxicity, including seizures, observed at this dose. In contrast, no embryo-fetal toxicities were observed when articaine and 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 MRHD based on body surface area).

In pre- and postnatal developmental studies subcutaneous administration of articaine hydrochloride to pregnant rats throughout gestation and lactation, at a dose of 80 mg/kg (approximately 2 times the MRHD based on body surface area) 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 MRHD on a mg/m^2 basis) did not produce these effects. A similar study using articaine and epinephrine (1:100,000) rather than articaine hydrochloride alone produced maternal toxicity, but no effects on offspring.

8.3 Nursing Mothers

It is not known whether Septocaine® is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Septocaine® is administered to a nursing woman. When using Septocaine®, nursing mothers may choose to pump and discard breast milk for approximately 4 hours (based on plasma half life) following an injection of Septocaine® (to minimize infant ingestion) and then resume breastfeeding.

8.4 Pediatric Use

Safety and effectiveness of Septocaine® in pediatric patients below the age of 4 years have not been established. Safety of doses greater than 7 mg/kg (0.175 mL/kg) in pediatric patients has not been established. Safety and effectiveness was established in clinical trials with 61 pediatric patients between the ages of 4 and 16 years administered articaine hydrochloride 4% and epinephrine 1:100,000 injections. Fifty-one of these patients received doses from 0.76 mg/kg to 5.65 mg/kg (0.9 to 5.1 mL) for simple dental procedures and 10 patients received doses between 0.37 mg/kg and 7.48 mg/kg (0.7 to 3.9 mL) for complex dental procedures. Approximately 13% of these pediatric patients required additional injections of anesthetic for complete anesthesia. Dosages in pediatric patients should be reduced, commensurate with age, body weight, and physical condition *[see Dosage and Administration (2.2)]*.

8.5 Geriatric Use

In clinical trials, 54 patients between the ages of 65 and 75 years, and 11 patients 75 years and over received Septocaine® containing 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 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 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 to 7 patients for simple procedures and doses of 1.12 mg/kg to 2 17 mg/kg (1.3 to 5.1 mL) were administered to 4 patients for complex procedures.

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.

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.

8.6 Renal/Hepatic Insufficiency

No studies have been performed with articaine hydrochloride 4% and epinephrine 1:200,000 injection or articaine hydrochloride 4% and epinephrine 1:100,000 injection in patients with renal or hepatic dysfunction *[see Warnings and Precautions (5.2)]*.

10 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 and Precautions (5.1, 5.2)]*.

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.

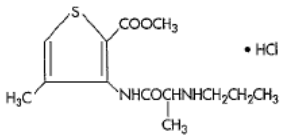
The first step in the management of convulsions, as well as hypo-ventilation, consists of immediate attention to the maintenance of a patent airway and assisted or controlled ventilation as needed. The adequacy of the circulation should be assessed. Should convulsions persist despite adequate respiratory support, treatment with appropriate anticonvulsant therapy is indicated. The practitioner should be familiar with the use of anticonvulsant drugs, prior to the use of local anesthetics. 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/or cardiac arrest. If cardiac arrest should occur, standard cardiopulmonary resuscitative measures should be instituted.

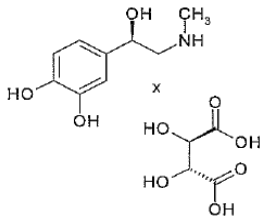
For additional information about overdose treatment, call a poison control center (**1-800-222-1222**).

11 DESCRIPTION

Septocaine® injection is a sterile, aqueous solution that contains articaine HCl 4% (40 mg/mL) and epinephrine bitartrate in an epinephrine 1:200,000 or epinephrine 1:100,000 strength. Articaine HCl is an amino amide local anesthetic, 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 following structural formula:



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 1:200,000 or 1:100,000 (expressed as free base). It has a molecular weight of 333.3 and the following structural formula:



Septocaine® contains articaine HCl (40 mg/mL), epinephrine (1:200,000 or 1:100,000) (as epinephrine bitartrate), 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.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Articaine HCl is an amide local anesthetic. 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. Epinephrine is a vasoconstrictor added to articaine HCl to slow absorption into the general circulation and thus prolong maintenance of an active tissue concentration.

12.2 Pharmacodynamics

Clinically, the order of loss of nerve function is as follows: (1) pain; (2) temperature; (3) touch; (4) proprioception; and (5) skeletal muscle tone.

The onset of anesthesia has been shown to be within 1 to 9 minutes of injection of Septocaine®. Complete anesthesia lasts approximately 1 hour for infiltrations and up to approximately 2 hours for nerve block.

Administration of Septocaine® 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 and Precautions (5.1)]*.

12.3 Pharmacokinetics

Absorption: Following dental injection by the submucosal route of an articaine solution containing epinephrine 1:200,000, 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 epinephrine 1:100,000 and 1:200,000, 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 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 epinephrine 1:100,000 and 1:200,000, 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*:* No studies have been performed to evaluate the pharmacokinetics of Septocaine® injection in pediatric subjects. There is insufficient information to determine whether the pharmacokinetics of Septocaine® injection differs by race.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies to evaluate the carcinogenic potential of articaine HCI 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 micronucleus tests (one with articaine and 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 articaine and epinephrine 1:100,000 administered subcutaneously in doses up to 80 mg/kg/day (approximately 2 times the MRHD based on body surface area).

14 CLINICAL STUDIES

Three randomized, double-blind, active-controlled studies were designed to evaluate effectiveness of Septocaine® containing 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 uncomplicated extractions, routine operative procedures, single apical resections, and single crown procedures, or 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® containing 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® containing epinephrine 1:100,000 versus Septocaine® containing 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® containing epinephrine 1:100,000 versus Septocaine® containing epinephrine 1:200,000 and 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® containing epinephrine 1:100,000 versus Septocaine® containing epinephrine 1:200,000 during bilateral maxillary periodontal surgeries in patients ranging from 21 to 65 years old. Septocaine® containing epinephrine 1:100,000 provided better visualization of the surgical field and less blood loss during the procedures. In a fourth study, designed to assess and compare cardiovascular safety, when the maximum dose of each formulation was administered, no clinically relevant differences in blood pressure or heart rate between formulations were observed.

15 REFERENCES

Kaplan, EL, editor. Cardiovascular disease in dental practice. Dallas; American Heart Association; 1986.

16 HOW SUPPLIED/STORAGE AND HANDLING

Septocaine® (articaine HCl and epinephrine) Injection is available in 1.7 mL single use glass cartridges, packaged in boxes of 50 cartridges in the following two strengths:

- Septocaine® containing articaine HCl 4% (40 mg/mL) and epinephrine 1:200,000 (as epinephrine bitartrate 0.009 mg/mL) (NDC 0362-9048-02)
- Septocaine® containing articaine HCl 4% (40 mg/mL) and epinephrine 1:100,000 (as epinephrine bitartrate 0.018 mg/mL) (NDC 0362-9049-02)

Storage and Handling

Store at controlled room temperature 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 Freeze.

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.

17 PATIENT COUNSELING INFORMATION

***Loss of Sensation and Muscle Function*:**

- Inform patients in advance of the possibility of temporary loss of sensation and muscle function following infiltration and nerve block injections [*see Adverse Reactions (6.2)*].
- Instruct patients not to eat or drink until normal sensation returns.

Manufactured for Septodont
Louisville, CO 80027
by NOVOCOL Pharmaceutical of Canada Inc.
Cambridge, Ontario, Canada N1R 6X3

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20971/S021

OTHER REVIEW(S)

REGULATORY PROJECT MANAGER LABELING REVIEW (PHYSICIAN LABELING RULE)

Amendment to RPM Labeling Review

Division of Anesthesia, Analgesia, and Rheumatology Products

Application Number: NDA 020971/SRL-021

Name of Drug: Septocaine® (articaine HCl and epinephrine) Injection
Articaine hydrochloride 4% and epinephrine 1:200,000 or
Articaine hydrochloride 4% and epinephrine 1:100,000

Applicant: Deproco, Inc.

Material Reviewed:

Submission Date(s): June 29, 2009

Receipt Date(s): June 30, 2009

Submission Date of Structure Product Labeling (SPL): June 30, 2009

Type of Labeling Reviewed: WORD

Reviews Completed:
Ayanna Augustus, Ph.D., Regulatory Project Manager, December 16, 2009
Parinda Jani, Chief, Project Management Staff, -concur
Bindi Nikhar, M.D., Clinical Team Leader, -concur
Dan Mellon, Ph.D., Pharmacology/Toxicology Team Leader -concur
Srikanth Nallani, Clinical Pharmacology Reviewer -concur
Elsbeth Chikhale, CMC Reviewer –concur

Mathilda Fienkeng, Regulatory Reviewer, DDMAC, November 11, 2009

Background and Summary

Deproco submitted their package insert for Septocaine® (articaine HCl and epinephrine) Injection, in physicians labeling rule (PLR) format to comply with the requirements set forth in 21 CFR 201.56, and 201.57.

Changes were made to the **CONTRAINDICATIONS, sections of the Package Insert .**

Review

Please note that the Division has amended the following sections of the label since the prior RPM review was finalized on January 5, 2010.

CONTRAINDICATIONS:

(b) (4)

Septocaine is contraindicated in patients who are hypersensitive to products containing sulfites. Products containing sulfites may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. Sulfite sensitivity is seen more frequently in asthmatic than in non-asthmatic people *[see Warnings and Precautions (5.5)]*.

Recommendations

The package insert for Septocaine® in PLR format is considered new labeling. This label is recommended for approval.

Ayanna Augustus, Ph.D.
Regulatory Project Manager

Supervisory Comment/Concurrence: **see attached email**

Parinda Jani
Chief, Project Management Staff

Drafted: AA/01/26/10
Revised/Initialed:
Finalized:
Filename: CSO Labeling Review Template (updated 1-16-07).doc
CSO LABELING REVIEW OF PLR FORMAT

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20971	SUPPL-21	DEPROCO INC	SEPTOCAINE

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/s/

AYANNA S AUGUSTUS
01/29/2010

REGULATORY PROJECT MANAGER LABELING REVIEW (PHYSICIAN LABELING RULE)

Division of Anesthesia, Analgesia, and Rheumatology Products

Application Number: NDA 020971/SRL-021

Name of Drug: Septocaine® (b) (4)
Articaine hydrochloride 4% and epinephrine 1:200,000 or
Articaine hydrochloride 4% and epinephrine 1:100,000

Applicant: Deproco, Inc.

Material Reviewed:

Submission Date(s): June 29, 2009

Receipt Date(s): June 30, 2009

Submission Date of Structure Product Labeling (SPL): June 30, 2009

Type of Labeling Reviewed: WORD

Reviews Completed:
Ayanna Augustus, Ph.D., Regulatory Project Manager, December 16, 2009
Parinda Jani, Chief, Project Management Staff, -concur
Bindi Nikhar, M.D., Clinical Team Leader, -concur
Dan Mellon, Ph.D., Pharmacology/Toxicology Team Leader -concur
Srikanth Nallani, Clinical Pharmacology Reviewer -concur
Elsbeth Chikhale, CMC Reviewer –concur

Mathilda Fienkeng, Regulatory Reviewer, DDMAC, November 11, 2009

Background and Summary

Deproco submitted their package insert for Septocaine® (articaine HCl and epinephrine) Injection, in physicians labeling rule (PLR) format to comply with the requirements set forth in 21 CFR 201.56, and 201.57.

Changes were made to the product name to clarify that the trade name referred to the two drug substances, articaine HCl and epinephrine.

Changes were also made **to INDICATIONS AND USAGE, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, and ADVERSE REACTIONS sections of the Package Insert.** Editorial changes were made to improve the readability and to minimize redundancy.

Review

Please note that the Division's proposed omissions are indicated by strikeovers, inclusions by underlined text.

PRODUCT NAME:

~~SEPTOCAINE® WITH EPINEPHRINE 1:100,000; SOLUTION~~
~~SEPTOCAINE® WITH EPINEPHRINE 1:200,000; SOLUTION~~
~~(articaine hydrochloride 4% (40 mg/mL) with epinephrine 1:100,000 or 1:200,000 injection~~

Septocaine® (b) (4)
Articaine hydrochloride 4% and epinephrine 1:200,000
Articaine hydrochloride 4% and epinephrine 1:100,000

INDICATIONS AND USAGE:

(b) (4)

CONTRAINDICATIONS:

(b) (4)

WARNINGS AND PRECAUTIONS:

5.5 Anaphylaxis and Allergic-Type Reactions

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.

ADVERSE REACTIONS:

6.2 Postmarketing Experience

Hypoesthesia has been reported with use of articaine, especially in pediatric age groups, which is usually reversible. Prolonged numbness can result in soft tissue injuries such as that of the lips and tongue in these age groups.

Ischemic injury and necrosis has been described following use of articaine with epinephrine and has been postulated to be due to vascular spasm of terminal arterial branches.

Paralysis of ocular muscles has been reported, especially after posterior, superior alveolar injections of articaine during dental anesthesia. Symptoms include diplopia, mydriasis, ptosis and

difficulty in abduction of the affected eye. These symptoms have been described as developing immediately after injection of the anesthetic solution and persisting one minute to several hours, with generally complete recovery.

Recommendations

The package insert for Septocaine® in PLR format is considered new labeling. This label is recommended for approval.

_____
Ayanna Augustus, Ph.D.
Regulatory Project Manager

Supervisory Comment/Concurrence:

_____
Parinda Jani
Chief, Project Management Staff

_____
Elsbeth Chikhale, Ph.D.
CMC Reviewer

_____
Dan Mellon, Ph.D.
Pharmacology/Toxicology Team Leader

_____
Srikanth Nallani, Ph.D.
Clinical Pharmacology Reviewer

_____
Bindi Nikhar, M.D.
Clinical Team Leader

Drafted: AA/11/3/09
Revised/Initialed: RDM 12/22/09
Finalized:
Filename: CSO Labeling Review Template (updated 1-16-07).doc
CSO LABELING REVIEW OF PLR FORMAT

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20971	SUPPL-21	DEPROCO INC	SEPTOCAINE

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/s/

AYANNA S AUGUSTUS
12/29/2009

PARINDA JANI
12/30/2009

ELSBETH G CHIKHALE
12/30/2009

RICHARD D MELLON
01/03/2010

SRIKANTH C NALLANI
01/04/2010

BINDI M NIKHAR
01/05/2010

MEMORANDUM

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

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

Date: November 3, 2009

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

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

Subject: **DDMAC draft labeling comments**
NDA 20-971 Septocaine® (b) (4) (b) (4)

DDMAC has reviewed the proposed product labeling (PI) for Septocaine® (b) (4) (Septocaine) submitted for consult on September 22, 2009.

The following comments are provided using the proposed PI sent via email on September 22, 2009 by Ayanna Augustus. If you have any questions about DDMAC's comments, please do not hesitate to contact me at 301 796 3692 or mathilda.fienkeng@fda.hhs.gov

7 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20971	SUPPL-21	DEPROCO INC	SEPTOCAINE

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/s/

MATHILDA K FIENKENG
11/03/2009

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20971/S021

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Augustus, Ayanna

From: Roca, Rigoberto A
Sent: Tuesday, January 26, 2010 10:12 AM
To: Simone, Arthur; Nikhar, Bindi; Jani, Parinda; Augustus, Ayanna; Compton, Kimberly
Subject: RE: Septocaine PLR

sounds like we are all in agreement....their proposal is ok.

Rigo

From: Simone, Arthur
Sent: Tuesday, January 26, 2010 9:38 AM
To: Nikhar, Bindi; Jani, Parinda; Augustus, Ayanna; Compton, Kimberly
Cc: Roca, Rigoberto A
Subject: RE: Septocaine PLR

I agree too. Seems we would have to list all the other ingredients for people to be able to apply the contraindication in a meaningful fashion. The sulfites are known allergens and worth mentioning by name.

Thanks.

Art

From: Nikhar, Bindi
Sent: Monday, January 25, 2010 8:53 PM
To: Jani, Parinda; Augustus, Ayanna; Compton, Kimberly
Cc: Roca, Rigoberto A; Simone, Arthur
Subject: RE: Septocaine PLR

Agree with the sponsor's rationale. Should be okay to include only sulfite hypersensitivity in the 'Highlights' section.

Thanks,

Bindi

From: Jani, Parinda
Sent: Monday, January 25, 2010 4:41 PM
To: Augustus, Ayanna; Compton, Kimberly
Cc: Nikhar, Bindi; Roca, Rigoberto A; Simone, Arthur
Subject: RE: Septocaine PLR

I think it is OK, but you all need to weigh in.

From: Augustus, Ayanna
Sent: Monday, January 25, 2010 4:35 PM
To: Compton, Kimberly
Cc: Nikhar, Bindi; Roca, Rigoberto A; Simone, Arthur; Jani, Parinda

Subject: FW: Septocaine PLR

Thanks Kim. I've cc'ed Rigo, Art, Bindi and Parinda on this email. The sponsor proposes amending the contraindications section of the highlights to read Known hypersensitivity to sulfite (4). Please weigh-in on their rationale. Since there haven't been any reports of (b) (4) perhaps this suggest should be considered.

Thanks,
Ayanna

From: Compton, Kimberly
Sent: Monday, January 25, 2010 4:22 PM
To: Augustus, Ayanna
Subject: FW: Septocaine PLR

Here the firm's reply to our proposed label change. Do we send to Art, Rigo, and Bindi, or are there more that need to see?

From: Matelski, Wayne H. [mailto:Matelski.Wayne@ARENTFOX.COM]
Sent: Monday, January 25, 2010 4:17 PM
To: Compton, Kimberly
Subject: FW: Septocaine PLR

Dear Kim,

Thank you for your email of 6:06 pm Friday. You DO work long hours.

We have reviewed the proposed change with our client. Our only concern is that the statement added to the Highlights section describes hypersensitivity (b) (4) For this reason, we would like to propose that the Highlight section be changed to, "Known hypersensitivity to sulfite (4)."

Please let me know if you would like to discuss this further or if you have any questions.

Thank you.

Sincerely,
Wayne and Brian

Wayne H. Matelski
Brian P. Waldman
Partners

Arent Fox LLP | Attorneys at Law
1050 Connecticut Avenue, NW
Washington, DC 20036-5339

202.857.6340 DIRECT | 202.857.6395 FAX
matelski.wayne@arentfox.com | www.arentfox.com

From: Compton, Kimberly [mailto:Kimberly.Compton@fda.hhs.gov]
Sent: Friday, January 22, 2010 6:06 PM
To: Matelski, Wayne H.; Waldman, Brian
Subject: Septocaine PLR

HI Wayne and Brian,

We are trying to complete the PLR conversion supplement for Septocaine and the team has made a last-minute change to the Contraindications section to include language to address known hypersensitivity to sulfites and would like to convey these to the sponsor.

We hope that this change will not be objectionable to since a similar statement is in the current label, but please let me know by COB Monday if they do have any issues with this change. I apologize for the last minute change.

<<Septocaine PLR 01-22-10.DOC>>

Thank you,

Kim

Kimberly Compton, R.Ph.

Regulatory Project Manager

Division of Anesthesia, Analgesia, and Rheumatology Products

Center for Drug Evaluation and Research

Food and Drug Administration

Bldg. 22, Rm 3161

10903 New Hampshire Ave

Silver Spring, MD 20993

301-796-1191 (phone)

Augustus, Ayanna

From: Compton, Kimberly
Sent: Wednesday, October 21, 2009 5:48 PM
To: Simone, Arthur; Nikhar, Bindi
Cc: Roca, Rigoberto A; Augustus, Ayanna
Subject: FW: Septocaine labeling for S-021
Attachments: Scan001.PDF; 2551-2.pdf; 2593-0.pdf

Hi folks,

Ayanna FWD me the finalized version of the labeling you've been working on for Septocaine to share with the firm. I did and their responses are below. They seem quite extensive (or at least high in number). Would you prefer to review and respond by email or would you like to team to meet?

Also, who else needs to be included (i.e., who has been working with you on this PI)? I am a bit out of the stream on this one since Ayanna has been so helpful in working on this so much, so I am not quite sure.

Thanks
Kim

From: Matelski, Wayne H. [mailto:Matelski.Wayne@ARENTFOX.COM]
Sent: Wednesday, October 21, 2009 4:09 PM
To: Compton, Kimberly
Cc: Waldman, Brian
Subject: RE: Septocaine labeling for S-021

Dear Kim:

Thank you for sending to us the revised draft labeling for Septocaine®. While we are preparing a final draft revision of the proposed insert labeling, we would like to raise with you and the Division a few questions and issues first. The answers to these which will affect how we finalize the draft revision for the Agency's consideration.

(b) (4)

3 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

Arent Fox LLP | Attorneys at Law
1050 Connecticut Avenue, NW
Washington, DC 20036-5339
202.857.6340 DIRECT | 202.857.6395 FAX
matelski.wayne@arentfox.com | www.arentfox.com

From: Compton, Kimberly [mailto:Kimberly.Compton@fda.hhs.gov]
Sent: Tuesday, October 13, 2009 3:05 PM
To: Matelski, Wayne H.; Waldman, Brian
Subject: Septocaine labeling for S-021

Dear Wayne and Brian,

Enclosed you will find revised labeling for Septocaine in clean and tracked changes mode. Please note that although there appear to be a number of changes to the package insert, the majority of these changes are formatting in nature, and were made to improve the readability of the label and ensure that all of the information about the Septocaine products are placed in the appropriate sections of the label. Please review the revised labels and email final draft product labeling by COB, October 21, 2009. Please send labeling in clean and track changes mode as WORD files.

<<Septocaine Draft PLR 101309.DOC>> <<Septocaine Draft PLR 101309 clean.DOC>>

Please let me know if you have any questions about our request.

Thanks

Kim

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20971	SUPPL-21	DEPROCO INC	SEPTOCAINE

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/s/

AYANNA S AUGUSTUS
12/11/2009

Augustus, Ayanna

From: Compton, Kimberly
Sent: Friday, December 04, 2009 5:47 PM
To: Augustus, Ayanna
Subject: FW: Septocaine Labeling
Attachments: Sponsor Revisions to Septocaine PLR_Clean Version.doc; Sponsor Revisions to Septocaine PLR_Redline.DOC

Hi Ayanna,

I would sent this to the team directly, but not sure who exactly gets it so I will pass to you and either you can send or I can if you tell me whose been working on it, etc.

Thanks!
-Kim

From: Matelski, Wayne H. [mailto:Matelski.Wayne@ARENTFOX.COM]
Sent: Friday, December 04, 2009 3:33 PM
To: Compton, Kimberly
Cc: Waldman, Brian
Subject: RE: Septocaine Labeling

Dear Kim:

Thank you for sending to us the revised draft labeling for Septocaine®. We appreciate that the Agency reviewers addressed the questions that we raised in our submission of October 21st. We now have had a chance to review the revised draft labeling and have only a few remaining questions and comments. (See also the attached mark-up of the draft labeling.)

1. Indications and Usage Section

(b) (4)

[redacted]

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(b) (4)

6. Typographical Errors

We have made these changes in the revised draft labeling that is attached hereto.

7. Format Change

We noticed that in the draft that you forwarded, the format had been changed from a two-column format to a one-column format. We assume that this change was made to facilitate our review of the changes and that we are free to select either format, but we wanted to confirm this point with you.

Please feel free to call Brian Waldman or me to discuss these issues further if you so desire.

Once again, I wanted to thank you and the Division for your consideration of these matters.

Sincerely,
Wayne

Wayne H. Matelski
Partner

Arent Fox LLP | Attorneys at Law
1050 Connecticut Avenue, NW
Washington, DC 20036-5339
202.857.6340 DIRECT | 202.857.6395 FAX
matelski.wayne@arentfox.com | www.arentfox.com

From: Compton, Kimberly [mailto:Kimberly.Compton@fda.hhs.gov]
Sent: Tuesday, November 24, 2009 12:24 PM
To: Matelski, Wayne H.; Waldman, Brian
Subject: FW: Septocaine Labeling

HI Wayne and Brian,

Attached is the draft labeling in clean and tracked changes mode for Septocaine. Please share it with the sponsor. In addition, we are also sending an attachment which contains the team's response to the sponsors' comments.

We request reply with final draft labeling in clean and tracked changes mode by, COB,

Friday, December 5th.

Please let me know if there are any questions. I will be out of the office the rest of the week after today, but returning on Monday.

Have a Happy Thanksgiving.

Thanks,

Kim

<<Septocaine Draft PLR 111609.DOC>> <<Septocaine Draft PLR 111609 clean.DOC>> <<Sponsor Comments on Revised Septocaine label b.pdf>>

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20971	SUPPL-21	DEPROCO INC	SEPTOCAINE

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/s/

AYANNA S AUGUSTUS
12/11/2009

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

REQUEST FOR CONSULTATION

TO *(Office/Division)*: DDMAC/ Mathilda Fienkeng, Regulatory Reviewer Officer	FROM *(Name, Office/Division, and Phone Number of Requestor)*: Ayanna Augustus, Project Manager, DAARP

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
9/22/09		20-971	PLR labeling	June 29, 2009

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Septocaine	standard	Dental anesthesia	11/13/09

NAME OF FIRM: Deproco, Inc

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☒ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: This supplement contains the Septocaine package insert in PLR format. Please review the package insert for promotional material. Electronic copies of the label can be found in the EDR: **\\FDSWA150\NONECTD\N20971\S_021\2009-06-29**

Please note that the review team has revised this label and the final draft is attached (in track changes mode). Please contact Ayanna Augustus if you need addition information (6-3980).

SIGNATURE OF REQUESTOR	METHOD OF DELIVERY (Check one)
Ayanna Augustus	☒ DARRTS ☐ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20971	SUPPL-21	DEPROCO INC	SEPTOCAINE

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/s/

AYANNA S AUGUSTUS
11/02/2009

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

REQUEST FOR CONSULTATION

TO *(Office/Division)*: DDMAC/ Mathilda Fienkeng, Regulatory Reviewer Officer	FROM *(Name, Office/Division, and Phone Number of Requestor)*: Ayanna Augustus, Project Manager, DAARP

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
9/22/09		20-971	PLR labeling	June 29, 2009

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Septocaine	standard	Dental anesthesia	11/13/09

NAME OF FIRM: Deproco, Inc

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☒ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

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AYANNA S AUGUSTUS
09/22/2009