

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-010

PHARMACOLOGY REVIEW(S)



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

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER: 22-010
SERIAL NUMBER: 000
DATE RECEIVED BY CENTER: September 30, 2005
PRODUCT: Septocaine ← (Articaine hydrochloride 4% (40 mg/mL) with Epinephrine 1:200,000 Injection)
INTENDED CLINICAL POPULATION: Induction of anesthesia by infiltration and nerve block
SPONSOR: Deproco, Inc.
DOCUMENTS REVIEWED: NDA submission
REVIEW DIVISION: Division of Anesthesia, Analgesia, and Rheumatology Products (HFD-170)
PHARM/TOX REVIEWER: Mamata De, Ph.D.
PHARM/TOX SUPERVISOR: R. Daniel Mellon, Ph.D.
DIVISION DIRECTOR: Bob A. Rapaport, M.D.
PROJECT MANAGER: Allison Meyer

Date of review submission to Division File System (DFS): March 29, 2006

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EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability

From the nonclinical pharmacology toxicology perspective, NDA 22-010 is recommended for Approval.

B. Recommendation for nonclinical studies

None.

C. Recommendations on labeling

The labeling below was submitted by the Sponsor on 11/1/2005. There are not alterations to the existing labeling at this time.

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 micronucleus tests (one with Septocaine® — and one with articaine HCl alone) showed no mutagenic effects. No effects on male or female fertility were observed in rats for Septocaine® — administered subcutaneously in doses up to 80 mg/kg/day (approximately two times the maximum male and female recommended human dose on a mg/m² basis).

Pregnancy: Teratogenic Effects-Pregnancy Category C.

In developmental studies, no embryofetal toxicities were observed when Septocaine® — 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/m² basis). In rabbits, 80 mg/kg (approximately 4 times the maximum recommended human dose on a mg/m² 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/m² 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/m² basis) did not produce these effects. A similar study using Septocaine® — (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®

should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings

The Sponsor submitted two publications from the public domain in support of this NDA application. All other data were previously submitted and reviewed for NDA 20-971. Ribeiro et al. (2003) compared the potential local tissue toxicity of articaine with that of bupivacaine, lidocaine and mepivacaine using a rat model. Doğan et al. (2003) compared the potential local toxicity of articaine and lidocaine with specific emphasis on wound healing.

The report by Ribeiro et al. noted that the local tissue reaction to articaine, under the conditions of the assay, did not generally differ from the reactions produced by the other local anesthetics tested. However, the articaine solution was noted to show evidence of some cellular necrosis that was not noted with the other test solutions.

Doğan et al. (2003) report that 4% articaine injections in the rat resulted in greater local tissue toxicity than 2% lidocaine injections. Likewise, the articaine treatment resulted in greater impairment of wound healing as measured by tensile strength compared to lidocaine treatment. Doğan et al. also noted some evidence of necrotic regions at the incision region from two animals in the articaine treatment group. Necrosis was not reported in any of the control or lidocaine treated animals. The authors suggest that the higher concentration of articaine (4%) compared to lidocaine likely contributed to the greater toxicity noted.

The findings reported by Ribeiro and Doğan support the conclusion that 4% articaine solution produced greater local tissue toxicity than a 2% lidocaine solution containing comparable levels of epinephrine. As the concentration of vasoconstrictor can increase the potential local tissue toxicity of a local anesthetic by retaining the anesthetic in the local environment for a longer duration, the proposed drug formulation containing lower levels of epinephrine that is the subject of the current NDA should result in less local tissue toxicity than the approved drug product. Assuming there are no clinical data suggesting a significant local tissue reaction associated with the clinical use of the approved drug product, the findings reported in Robiero et al. (2003) and Doğan et al. (2003) do not appear to be clinically significant.

B. Pharmacologic activity

Articaine hydrochloride is an FDA approved local anesthetic of the amino amide class. Local anesthetics blocks the generation of the conductive nerve impulses presumably by increasing the threshold for electrical excitation in the nerve by slowing the propagation of nerve impulse and by reducing the rate of rise of the action potential. In general the progression of anesthesia is related to diameter, myelination and the conduction velocity of the affected nerve fibers. Clinically, the order of loss of nerve function is as follows, pain temperature, touch, proprioception and skeletal muscle tone. The epinephrine is a vasoconstrictor added to articaine HCl to slow absorption into the general circulation.

C. Nonclinical safety issues relevant to clinical use

The two literature references provided suggest that articaine hydrochloride 4% may be associated with slightly greater local tissue toxicity than with other local anesthetics used for dental applications. Although the nonclinical data describe real findings, unless there are clinical data suggesting unacceptable increased local tissue toxicity with the approved drug formulation, the new nonclinical data do not appear to be relevant to the clinical use of this drug product.

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2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 22-010
Review number: 1
Sequence number/date/type of submission: 000/ September 30, 2005/ NDA
Information to sponsor: Yes () No (X)
Sponsor and/or agent: Deproco Inc.
 New Castle, DE 19720

Manufacturer for drug substances:

Articaine hydrochloride:

Epinephrine:

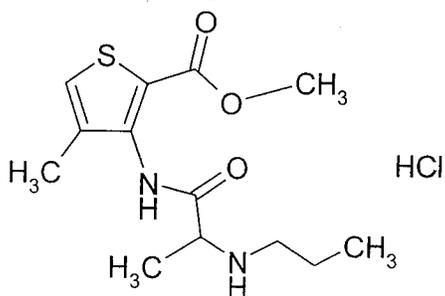


Reviewer name: Mamata De, Ph.D.
Division name: Division of Anesthesia, Analgesia, and Rheumatology Products
HFD #: 170
Review completion date: February 3, 2006

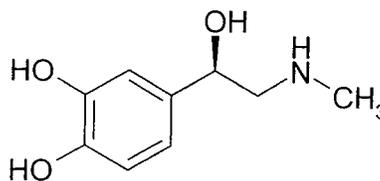
Drug:

Trade name: Septocaine (also: Carticaine, Ultracain, Ultracaine)
Generic name: Articaine Hydrochloride 4% with epinephrine 1:200,000 injection
Code name: HOE 40045; HOE 045
Chemical name: Methyl 4-methyl-3-((1-oxo-2-(propylamino)propyl)amino)-2-thenoate monohydrochloride
CAS registry number: 23964-57-0
Molecular formula/molecular weight: C₁₃H₂₀N₂O₃S•HCl / 320.84

Structures:



Articaine hydrochloride



Epinephrine

Relevant INDs/NDAs/DMFs:

Appl No	Drug	Indication	Division	Status	Applicant
NDA 20-971	Septocaine	For infiltration or nerve block anesthesia for dentistry	170	AP 3-Apr-2000	Deproco, Inc.
IND 51,721	Septanest 1:100,000/1:200,000 articaine:epinephrine	For infiltration or nerve block anesthesia for dentistry	170	Active	Deproco, Inc.

DMF	Drug	DMF Holder
	Articaine hydrochloride	
	Articaine hydrochloride	
	Epinephrine bitartrate	

Drug class: Local anesthetic of the amide-type and is a racemic mixture.

Intended clinical population: Patients requiring local anesthesia for dental surgery

Clinical formulation: Like Septocaine 1:100,000, the Septocaine 1:200,000 drug product will be provided in a 1.7 mL glass cartridge, in boxes of 50 cartridges. The product is formulated with a 15% overage of epinephrine. The composition of the drug product is provided in the Sponsor's table below:

COMPONENTS	Quantity per 1 mL	Quantity per 1.7 mL
Articaine hydrochloride	40.0 mg	
Epinephrine bitartrate, USP (Expressed as base)		
Sodium Chloride, USP	1.60 mg	
Sodium metabisulphite, NF	0.5 mg	
Sodium hydroxide solution, NF		

Based on the previous findings of safety by the Agency for NDA 20-971, there are no pharmacology toxicology concerns with the current different dose proposed in NDA 22-010.

Route of administration: injection

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Data reliance: Except as specifically identified below, all data and information discussed below and necessary for approval of NDA 22-010 are owned by Deproco, Inc. or are data for which Deproco, Inc. has obtained a written right of reference. Any information or data necessary for approval of NDA 22-010 that Deproco, Inc. does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that Deproco, Inc. does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of NDA 22-010.

Specifically, the Sponsor has provided the following comment regarding patent certification:

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

The Sponsor is primarily relying upon the Agency's previous findings of safety and efficacy for the Sponsor's previous NDA application for Septocaine — (NDA 20-971), which is identical to the current product with the exception that the current product contains only half of the epinephrine content compared to the approved product.

Studies reviewed within this submission:

The sponsor only submitted two references from the published literature for the nonclinical submission (Ribeiro, Jr. et al., 2003; Dogan et al., 2003).

1. Doğan N, Üçok C, Korkmaz C, Üçok Ö And Karasu Ha (2003) The Effects Of Articaine Hydrochloride On Wound Healing: An Experimental Study. J Oral Maxillofac Surg 61:1467-1470.
2. Ribeiro Pd, Jr., Sanches Mg And Okamoto T (2003) Comparative Analysis Of Tissue Reactions To Anesthetic Solutions: Histological Analysis In Subcutaneous Tissue Of Rats. Anesth Prog 50:169-180.

Studies not reviewed within this submission: The Sponsor's data previously submitted in support of NDA 20-971 was reviewed by Dr. Goheer and not re-evaluated for the current NDA submission. The reader is referred to Dr. Goheer's review for details related to the initial approval of Septacaine —.

2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary

When applied locally to nerve tissue in appropriate concentrations, local anesthetics reversibly block the action potentials responsible for nerve conduction. A local anesthetic in contact with a nerve trunk can cause both sensory and motor paralysis in the area innervated. The action is reversible at clinically relevant concentrations; complete recovery in nerve function occurs with no evidence of damage to nerve cell fibers or cells.

Local anesthetics block conduction by decreasing or preventing the large transient increase in the permeability of excitable membranes to Na^+ that normally is produced by a slight depolarization of the membrane due to direct interaction with voltage-gated Na^+ channels. Local anesthetics can also bind to other membrane proteins such as K^+ channels. However, blockade of conduction is not accompanied by any large or consistent change in resting membrane potential due to block of K^+ channels since the interaction of local anesthetics with K^+ channels requires higher drug concentrations.

2.6.2.2 Primary pharmacodynamics

Mechanism of action: Local anesthetics block the generation and conduction of nerve impulses in excitable tissues by decreasing or preventing the large transient increase in the permeability of the membrane to sodium ions. Local anesthetics bind directly to voltage-gated sodium channels from the inside of the membrane. The degree of block produced by local anesthetics is dependent upon how the rate of nerve stimulation and on its resting membrane potential. Local anesthetics are only able to bind to sodium channels in their charged form and when the sodium channels are open. In this situation, the local anesthetic is able to bind more tightly to and stabilize the sodium channel. Differences in pKa, lipid solubility, and molecular size influence the binding of local anesthetics to sodium channels. The basic structure of a sodium channel subunit is depicted below:

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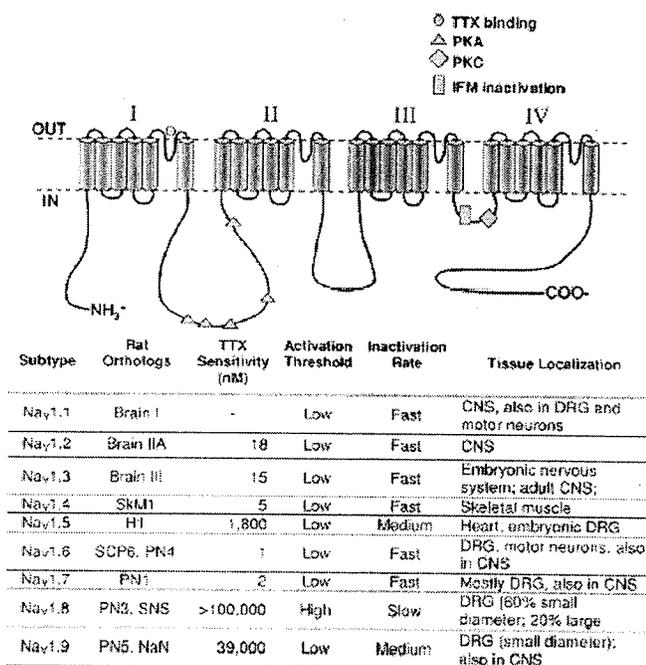


Figure 1 Schematic secondary structure of the family of VGSCs, their classification, tissue distribution, and functional characteristics.

shorter distances and these fibers have longer action potentials allowing more of the local anesthetic to bind. Clinically, the loss of nerve function proceeds as loss of pain, temperature, touch, proprioception, and then skeletal muscle.

Drug activity related to proposed indication: Blockade of neuronal conduction prevents the action potential of sensory neurons and therefore blocks the transmission of pain signals to the CNS. Lidocaine and tetracaine blockade demonstrates both frequency and voltage-dependency. Both drugs block both open and inactivated Na^+ channels. The frequency dependence of this blockade makes smaller unmyelinated nerve fibers more sensitive to blockade than larger heavily myelinated fibers. Therefore, Type C fibers (dorsal root and sympathetic nerves) and Type B (preganglionic autonomic nerves) are blocked at lower concentrations than heavily myelinated Type A (alpha, beta, gamma and delta) fibers. Of the type A fibers, pain and temperature sensitive neurons (delta) are more susceptible to local anesthetics than muscle spindles (gamma), touch and pressure sensitive neurons (beta) which are, in turn, more sensitive than proprioception and motor neurons (alpha). This sensitivity also correlates with the diameter of the nerve fiber, with smaller fibers being more sensitive to the local anesthetic action.

2.6.2.3 Secondary pharmacodynamics

In addition to Na^+ channels, local anesthetics can bind to other membrane proteins. Specifically, local anesthetics have been shown to bind to K^+ channels, at higher concentrations.

In general, small nerve fibers are more sensitive to local anesthetics than large nerve fibers. However, myelinated fibers are blocked before non-myelinated fibers of the same diameter.

Autonomic fibers, small unmyelinated C fibers (mediating pain) and small myelinated $\text{A}\delta$ fibers (mediating pain and temperature sensation) are blocked before larger myelinated $\text{A}\gamma$, $\text{A}\beta$, or $\text{A}\alpha$ fibers (mediating touch, pressure, muscle and postural inputs). Small, sensory fibers are preferentially blocked since nerve conduction is more easily blocked over

In addition to blockade of sensory nerves, local anesthetics also interfere with the functioning of all organs which require the conduction of electrical impulses for their activity. These organs include the CNS, autonomic ganglia, neuromuscular junction and all forms of muscle, including cardiac.

2.6.2.4 Safety pharmacology

Formal safety pharmacology studies have not been conducted with articaine hydrochloride for this NDA, and are typically not required for drugs that have a long history of clinical use. However, extensive experience with local anesthetics has provided a clear understanding of the effects of these drugs on the critical systems of the body. Toxicity is due to an exaggerated pharmacological activity, primarily on the cardiovascular and central nervous system. Initial effects include mild hypertension and tachycardia, lightheadedness, mild agitation, and confusion. In severe cases this may progress to seizures, coma, respiratory depression, bradycardia, ventricular arrhythmias and asystole. Toxicity may result from an excessive dose, mistaken drug identity, enhanced drug absorption, inadvertent intravascular injection, altered protein binding, slowed redistribution and/or elimination.

2.6.2.5 Pharmacodynamic drug interactions

There were no nonclinical data provided with this NDA application.

2.6.3 PHARMACOLOGY TABULATED SUMMARY

There were no tabulated summary tables provided by the sponsor.

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

2.6.4.1 Brief summary

See original pharmacology toxicology review by Dr. Goheer.

2.6.4.2 Methods of Analysis

[see under individual study reviews]

2.6.4.3 Absorption

No studies were submitted.

2.6.4.4 Distribution

Tissue distribution studies were not submitted with this NDA. According to DrugDex Drug Evaluations database, articaine protein binding ranges from 50 to 80%. The

volume of distribution is 1 to 2 L/kg (Oertel & Richter, 1998; Oertel et al., 1997; Oertel et al., 1996).

2.6.4.5 Metabolism

Articaine is rapidly metabolized by plasma and tissue esterases to articainic acid (Oertel & Richter, 1998; Oertel et al., 1997; Oertel et al., 1996). Articainic acid is not pharmacologically active.

2.6.4.6 Excretion

Articaine is primarily excreted via the kidney as articainic acid and articainic acid glucuronide (Oertel et al., 1997).

2.6.4.7 Pharmacokinetic drug interactions

There were no nonclinical pharmacokinetic studies submitted.

2.6.4.8 Other Pharmacokinetic Studies

Not applicable.

2.6.4.9 Discussion and Conclusions

Not applicable.

2.6.4.10 Tables and figures to include comparative TK summary

Summary tables were not provided with this NDA submission.

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

Study Information	Major Findings in ADME Studies
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Distribution study in mini pig (published), S ³⁵ labeled ; IM and IV administration	Organs	After I.V. Injection 15 min (n=1) 48 hours (n=2)		After I.M. Injection 60 min. (n=1) 48 hours (n=2)	
	Brain	49.6	0.38	21.0	0.39
	Heart	39.2	1.01	25.0	0.76
	Lung	119.8	1.37	132.2	2.35
	Liver	145.0	2.74	59.6	3.30
	Spleen	76.7	1.09	35.6	1.40
	Right Kidney	498.4	3.86	208.6	3.16
	Left Kidney	470.4	2.97	157.1	3.25
	Diaphragm	35.3	0.62	16.6	0.62
	Muscle	40.6	0.42	34.7	0.50
	Abdominal Fat	2.5	0.95	8.3	0.95
	Dorsal Fat	30.0	1.26	16.1	0.67
	Whole Blood	27.2	1.18	16.0	0.81
AUC in rat (ug•min/mL)	Dose mg/kg/day	Day 1		Day 28	
		Males	Females	Males	Females
	25	99.5	97.1	52.5	63.6
	50	204.8	230.8	70.8	51.9
	100	372.4	372.4	89.6	81.9
AUC in dog (ug•min/ml)	Dose mg/kg/day	Day 1		Day 28	
		Males	Females	Males	Females
	20	151.9	101.9	175.0	123.9
	40	157.1	106.9	136.2	162.0
	80	209.4	293.0	494.7	331.3
T _{max} in rat and dog	20-40 min at day 1 and 10-20 mins at day 28				
C _{max} in rat and dog	Cmax (ug/mL)	Rat (NOEL dose-25 mg/kg/day)		Dog (NOEL dose-40 mg/kg/day)	
		1.9		2.2-2.7	
Metabolism	Not done w/the current formulation, however, noted articanic acid as major metabolite in rat and dog				
Excretion	Not done w/the current formulation, however, noted urine as major route of elimination in rat and dog				

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

The toxicology studies that were originally submitted with NDA 20-971 and reviewed by Dr. Goheer have been subsequently published in summary format (Leuschner & Leblanc, 1999).

No new toxicology studies were completed.

2.6.6.2 Single-dose toxicity

No new single-dose toxicology studies were submitted in support of this NDA.

2.6.6.3 Repeat-dose toxicity

No new repeat-dose toxicology studies were submitted in support of this NDA.

2.6.6.4 Genetic toxicology

No new genetic toxicology studies were submitted in support of this NDA. A total of 4 genetic toxicology studies were completed in support of the original NDA, as summarized in the table below, reproduced from (Leuschner & Leblanc, 1999).

Table 3: Design and conditions of genotoxicity studies of articaine HCl.

Type of study	Test system	Assay conditions	Dose range/concentration range
Gene mutation in bacteria	Salmonella typhimurium (TA 98, TA 100, TA 102, TA 1535 and TA 1537)	with and without metabolic activation	100 to 10 000 µg articaine HCl/plate
Gene mutation in vitro	V79 Chinese hamster lung cell line (CHL; HPRT test)	with and without metabolic activation	without metabolic activation: 125 to 1000 µg articaine HCl/ml (20-h exposure), 250 to 2000 µg articaine HCl/ml (4-h exposure) with metabolic activation: 500 to 3000 µg articaine HCl/ml (4-h exposure)
Chromosomal aberration in vitro	Chinese hamster ovary cells (CHO)	with and without metabolic activation	without metabolic activation: 125 to 1000 µg articaine HCl/ml (20-h exposure) with metabolic activation: 250 to 2000 µg articaine HCl/ml (4-h exposure)
Chromosomal aberration in vivo	Bone marrow cells (micronucleus test)	NMRI mouse, s.c. sampling times: 24, 48 and 72 h 5 ♂/5 ♀ per dose and sampling time	75 mg articaine HCl/kg b.w. s.c.

The results of these studies are summarized in the approved drug label for NDA 20-971 as follows:

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 micronucleus tests (one with Septocaine® and one with articaine HCl alone) showed no mutagenic effects.

2.6.6.5 Carcinogenicity

Long-term animal studies have not been completed to assess the carcinogenic potential of articaine hydrochloride or epinephrine bitartrate. Carcinogenicity studies are not required for acute drug products.

2.6.6.6 Reproductive and developmental toxicology

A total of 4 genetic toxicology studies were completed and submitted in support of NDA 20-971, as summarized in the table below, reproduced from (Leuschner & Leblanc, 1999).

Table 2: Design and conditions of reproduction toxicity studies of articaine HCl.

Type of study	Species and strain	Articaine HCl dose (mg/kg b.w./day)	Route of administration	Animals per dose	Treatment schedule
Fertility (Segment I)	Rat Sprague-Dawley	control ^{a)} 20, 40 and 80	s.c.	20/sex	males: 4-5 weeks before mating and during mating period females: 2-3 weeks before mating until day 7 of gestation
Embryotoxicity study (Segment II)	Rat Sprague-Dawley	control ^{a)} 20, 40 and 80	s.c.	20 females	from day 6 to day 17 of gestation
Embryotoxicity study (Segment II)	Rabbit Himalayan	control ^{a)} 20, 40 and 80	s.c.	16 females	from day 6 to day 20 of gestation
Peri- and postnatal toxicity (Segment III)	Rat Sprague-Dawley	control ^{a)} 20, 40 and 80	s.c.	20 females	from day 6 of gestation until the end of lactation

^{a)} aqua ad injectabilia.

The results of these studies are summarized in the approved drug label for NDA 20-971 as follows:

No effects on male or female fertility were observed in rats for Septocaine® — administered subcutaneously in doses up to 80 mg/kg/day (approximately two times the maximum male and female recommended human dose on a mg/m² basis).

Pregnancy: Teratogenic Effects-Pregnancy Category C.

In developmental studies, no embryofetal toxicities were observed when Septocaine® — 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/m² basis). In rabbits, 80 mg/kg (approximately 4 times the maximum recommended human dose on a mg/m² 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/m² 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/m² basis) did not produce these effects. A similar study using Septocaine® — (articaine hydrochloride and epinephrine 1:100,000) rather than articaine hydrochloride alone produced maternal toxicity, but no effects on offspring.

According to a search of the TERIS database (The Teratogen Information System) at the time of NDA review, "No epidemiological studies of congenital anomalies in children born to women given articaine during pregnancy have been reported."

2.6.6.7 Local tolerance

STUDY TITLE: Ribeiro, P.D., Jr., Sanches, M.G. and Okamoto, T. (2003) Comparative Analysis of Tissue Reactions to Anesthetic Solutions: Histological Analysis in Subcutaneous Tissue of Rats. *Anesth. Prog.* 50:169-180.

Parameters		Methods, Results & Conclusions							
Species		Male Wistar Rats, weighing Fisher F344 rats, weighing between 230 and 280 grams							
Treatment Groups		Group 1: 0.9% sodium chloride solution Group 2: 0.5% Bupivacaine hydrochloride (plus 1:200,000 epinephrine) Group 3: 4% Articaine hydrochloride (plus 1:100,000 epinephrine) Group 4: 2% Lidocaine without vasoconstrictor Group 5: 2% Mepivacaine (plus 1:100,000 epinephrine)							
Study Design		<ol style="list-style-type: none"> Under general anesthesia with thiopental sodium solution, the dorsal region of the rats was shaved, and two cutaneous incisions of approximately 1 cm were made at the mid sagittal region. Sterilized absorbent paper cones packed inside with polyethylene tubes (Nasogastric probe #4, Enbramed) were soaked in the drug solutions and implanted in the subcutaneous region. Tubes were introduced into subcutaneous tissue positioned approximately 2 cm from incisions. The surgical wound was sutured with non-absorbable 3-0 silk. 2 animals per group were euthanized at 1, 2, 5 and 10 days post implantation. Tissue specimens from the dorsal region were fixed in 10% formalin and evaluated microscopically. Under the light microscope, tissue reactions were analyzed via the Wolson and Seltzer criterion based on the number of inflammatory cells as follows: <ol style="list-style-type: none"> Mild: fewer than 100 inflammatory cells (in 10 different fields magnified 400 times) Moderate: between 100 and 500 cells Severe or Intense: over 500 cells Vascular neoformation and fibroblastic proliferation along the implant were assessed via the Spangberg Irritation Signal. 							
Results: Table 1. Location and Intensity of the Inflammatory Infiltrate									
Groups		1 Day		2 Days		5 Days		10 Days	
		Near	Distant	Near	Distant	Near	Distant	Near	Distant
I SAL	A	+++	++	+++	--	+	--	+	--
	C	++	+	--	+	--	+	--	+
II BUP	A	+++	+++	+++	--	+++	--	++	--
	C	+	+	--	++	++	+	--	++
III ART	A	++	+	+	--	++	--	+	--
	C	--	+	+	++	++	+	--	++

IV LIDO	A	++	--	++	--	+++	--	+	--
	C	+	+	+	++	--	++	--	+
V MEP	A	+++	--	+	++	--	--	+	--
	C	--	+	+	++	+	--	--	++

For comparison, the histological data were considered to be mild (+), moderate (++) and intense (+++), as per respective magnitudes. The absence of these elements is noted by the sign (--). SAL, indicates saline; BUP, bupivacaine; ART, articaine; LIDO, lidocaine; MEP, mepivacaine; A, acute; and C, chronic.

Table 2. Location and Intensity of Vascular Neof ormation and Fibroblastic Proliferation.

Groups		1 Day		2 Days		5 Days		10 Days	
		Near	Distant	Near	Distant	Near	Distant	Near	Distant
I SAL	V	--	+	--	+	--	++	--	++
	F	--	--	--	+	--	+++	--	+++
II BUP	V	--	--	--	++	--	+++	--	++
	F	--	--	--	+	--	+++	--	+++
III ART	V	--	--	--	--	--	+++	--	++
	F	--	--	--	+	--	+++	--	++
IV LIDO	V	--	--	--	++	--	++	--	+++
	F	--	--	--	--	--	++	--	+++
V MEP	V	--	+	--	+	--	+	--	+++
	F	--	--	--	+	++	++	--	+++

For comparison, the histological data were considered to be mild (+), moderate (++) and intense (+++), as per respective udes. The absence of these elements is noted by the sign (--). SAL, indicates saline; BUP, bupivacaine; ART, articaine; LIDO, lidocaine; MEP, mepivacaine; V, vascular; and F, fibroplastic.

Description of Histology	Day 1: Of all the test articles evaluated, only the articaine solution was noted show a "thin band of necrotic tissue" surrounding the implant.
Report Conclusions	"On the basis of the analysis of the histological results obtained from this study, - we can conclude that (a) the tested anesthetic solution presented different tissue reactions; (b) the bupivacaine group presented the most intense inflammatory reaction; (c) the articaine and mepivacaine groups generated similar inflammatory reactions; and (d) the lidocaine group presented the least intense inflammatory reaction."
Reviewer's Comment	The report noted that the local tissue reaction under the conditions of the assay, were overall not all that different between groups; however, the articaine solution was noted to show evidence of some cellular necrosis that was not noted with the other test solutions. As the current NDA actually contains less epinephrine than the previously approved drug product, and there have not been reports suggesting that there have been clinically significant delays in wound healing for Septocaine 100, the current drug product would likely have less local tissue toxicity. The findings are consistent with the slightly greater local tissue toxicity with the 4% articaine solution, perhaps due to the higher concentration of the local anesthetic used in this drug product. In the absence of any clinical data suggesting a significant local tissue reaction associated with the use of the drug product, the findings reported in Robiero et al. do not appear to be clinically significant.

2.6.6.8 Special toxicology studies

STUDY TITLE: Doğan N, Üçok C, Korkmaz C, Üçok Ö And Karasu Ha (2003) The Effects Of Articaine Hydrochloride On Wound Healing: An Experimental Study. *J Oral Maxillofac Surg* 61:1467-1470.

Parameters	Methods, Results & Conclusions
Species	Fisher F344 rats, weighing between 230 and 280 grams
Treatment Groups	Group 1: 2% Lidocaine (plus 1:100,000 epinephrine) Group 2: 4% Articaine hydrochloride (plus 1:100,000 epinephrine) Group 3: Saline solution Group 4: Control group (no injection)
Study Design	<ol style="list-style-type: none"> 1. Under general inhalation anesthesia, the dorsal region of the rats was shaved, sterilized with povidone-iodine and dried with sterile towels. 2. Solutions of 2.5 mL were injected into 4 separate locations on both sides of the incision line at a distance of at least 1 cm from the incision. 3. A 4 cm linear incision was made on the dorsal midline up to the muscular fascia. 4. The surgical wound was sutured with non-absorbable 3-0 silk. 5. No post-operative antibiotics were employed. 6. Animals were euthanized 7 days after the wound. 7. Tissue specimens from the dorsal region were fixed in 10% formalin and evaluated microscopically. 8. Under the light microscope, morphometric evaluation of newly formed collagen fibers was completed and the stage of wound healing was graded according to the following criteria: <ol style="list-style-type: none"> a. Stage 1: Stage of Inflammation b. Stage 2: Development of Granulation Tissue c. Stage 3: Development of Scar Tissue d. Stage 4: Completion of Epithelialization 9. All skin portions were subjected to breaking determination testing via a Lloyd LRX tensile and compression testing apparatus with wound strength expressed in Newtons.

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Group	Histologic Grade		BST (mean ± SD)
	Median	Mean (range)	
Control (n = 10)	4	3.7 (3-4)	12.41 ± 1.45
Saline solution (n = 10)	3	3.4 (3-4)	11.36 ± 1.30
Lidocaine (n = 10)	2	2.2 (1-3)*	8.29 ± 1.27*
Articaine (n = 10)	1	1.5 (1-3)†	5.57 ± 1.22*‡

*Differences between experimental groups with saline and control groups were statistically significant, $P < .01$.
 †Differences between lidocaine and articaine groups were statistically significant, $P < .05$.
 ‡Differences between lidocaine and articaine groups were statistically significant, $P < .001$.

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<p>Graph of Breaking Strength Test Results</p>	<p>FIGURE 4. Distribution of the results of the breaking strength test for the groups.</p>
<p>Report Conclusions</p>	<p>Although complete wound healing in the incision region was noted by day 7 in all treatment groups, there were significant differences between treatments. The document notes that some necrotic regions were observed at the incision region in 2 samples of the articaine hydrochloride group. The local tissue effects of articaine hydrochloride were statistically different from the effects of lidocaine in this study.</p> <p>However, the authors state that “our opinion is that this [effects of articaine] has no clinical importance.....the BST and histological effects at 7 days cannot imply any clinically relevant delayed wound healing. In light of the results of this study, AH can be regarded as a safe local anesthetic agent for surgery in the head and neck regions.”</p>
<p>Reviewer’s Comment</p>	<p>The report noted that the tissue toxicity due to local anesthetic agents has been reported to be greater when a vasoconstrictor is also injected due to the more prolonged local exposure to the local anesthetic. As the current NDA actually contains less epinephrine than the previously approved drug product, and there have not been reports suggesting that there have been clinically significant delays in wound healing for Septocaine 100, the current drug product would likely have less local tissue toxicity. Although academically interesting, the findings reported by Doğan et al. do not appear to be clinically significant.</p>

2.6.6.9 Discussion and Conclusions

The data submitted by the Sponsor in support of NDA 20-971 is also directly relevant for the current drug product. No additional toxicology studies were required for the current NDA.

2.6.6.10 Tables and Figures

Not provided.

2.6.7 TOXICOLOGY TABULATED SUMMARY

Summary tables were not provided by the sponsor of this NDA.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions: The local tissue toxicity and wound healing findings reported by Ribeiro and Doğan support the conclusion that 4% articaine solution produced greater local tissue toxicity than a 2% lidocaine solution containing comparable levels of epinephrine. As the concentration of vasoconstrictor can increase the potential local tissue toxicity of a local anesthetic by retaining the anesthetic in the local environment for a longer duration, the proposed drug formulation containing lower levels of epinephrine that is the subject of the current NDA should result in less local tissue toxicity than the approved drug product. Assuming there are no clinical data suggesting a significant local tissue reaction associated with the clinical use of the approved drug product, the findings reported in Robiero et al. (2003) and Doğan et al. (2003) do not appear to be clinically significant.

Unresolved toxicology issues (if any): None

Recommendations: From the nonclinical pharmacology toxicology perspective, NDA 22-010 may be approved.

Suggested labeling: No specific labeling changes are necessary at this time.

Signatures (optional):

Reviewer Signature _____

Supervisor Signature _____ Concurrence Yes ___ No ___

APPENDIX/ATTACHMENTS

Reference List

- Dogan, N., Ucok, C., Korkmaz, C., Ucok, O., & Karasu, H. A. (2003). The effects of articaine hydrochloride on wound healing: an experimental study. *J Oral Maxillofac.Surg*, 61, 1467-1470.
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- Oertel, R., Berndt, A., & Kirch, W. (1996). Saturable in vitro metabolism of articaine by serum esterases. Does it contribute to the persistence of the local anesthetic effect? *Reg Anesth*, 21, 576-581.
- Oertel, R., Rahn, R., & Kirch, W. (1997). Clinical pharmacokinetics of articaine. *Clin Pharmacokinet.*, 33, 417-425.
- Oertel, R. & Richter, K. (1998). Plasma protein binding of the local anaesthetic drug articaine and its metabolite articainic acid. *Pharmazie*, 53, 646-647.
- Ribeiro, P. D., Jr., Sanches, M. G., & Okamoto, T. (2003). Comparative analysis of tissue reactions to anesthetic solutions: histological analysis in subcutaneous tissue of rats. *Anesth Prog.*, 50, 169-180.

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/s/

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3/29/2006 01:53:14 PM
PHARMACOLOGIST

R. Daniel Mellon
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I concur.

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