CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-010

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 22-010	Submission Date(s): 09/29/2005
Brand Name	Septocaine —®
Generic Name	Articaine Hydrochloride and epinephrine Bitartarate
Reviewer	Srikanth C. Nallani, Ph.D.
Team Leader	Suresh Doddapaneni, Ph.D.
OCPB Division	Division of Clinical Pharmacology and Biopharmaceutics - 2
ORM Division	Division of Anesthesia, Analgesia, and Rheumatology Products
Sponsor	Deproco, Inc.
Relevant IND(s)	51,721
Relevant NDA(s)	20-971
Submission Type; Code	Original NDA; New Formulation Standard Review (5S)
Formulation; Strength(s)	Articaine HCl 4% , epinephrine 1: 200,000
Indication	For infiltration or nerve block anesthesia for dentistry
Dosage and Administration	—-100 mg for infiltration; 20-136 mg for nerve block; 40-204 mg for oral surgery

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1 Executive Summary

1.1 Recommendation

The submission consists of four Phase 3 clinical trials conducted under IND 51,721 comparing Septocaine® ~ and Septocaine® — (subject of NDA 20-971). Of these, Study ART-03-001 compared the peak plasma concentration of articaine achieved following administration of Septocaine®— and Septocaine®—. The submission is acceptable from a Clinical Pharmacology and Biopharmaceutics perspective provided that a mutually satisfactory agreement can be reached between the Agency and the sponsor with regard to labeling changes.

1.2 Phase IV Commitments

None

1.3 Summary of CPB Findings

Current submission pertains to Septocaine® — containing articaine HCl (4%) and epinephrine bitartarate (1:200,000). Septocaine®, containing articaine HCl (4%) and epinephrine bitartarate (1:100,000), was approved in 1997 under NDA 20-971. With the submission of a new formulation, the sponsor is seeking approval to change the trade name of currently approved Septocaine® to Septocaine® —. The difference between the two formulations in relation to articaine HCl is the strength of epinephrine, which is present in the ratio of 1:100,000 in Septocaine® —or 1:200,000 in Septocaine® — Epinephrine is a vasoconstrictor that in appropriate concentrations will serve to localize articaine at the site of application and slowing down the escape into systemic circulation.

When NDA 20-971 was submitted by this sponsor in March of 1998, approval was sought for both the above mentioned Septocaine® products. However, the Agency approved only the higher epinephrine strength (1:100,000) 4% articaine HCl formulation (Septocaine® —) as sufficient information was not available in the NDA (among other things) to determine (a) the situations when each of the products should be used (2) that the lower strength epinephrine concentration is not inferior to the higher strength concentration, and (c) that the lower strength of epinephrine has a less safety profile. In this application, data from three clinical studies and one pharmacokinetic study (ART-03-001) was submitted to address the above issues. This submission was originally submitted as a supplement (S-014) to NDA 20-971. However, this was administratively split into new NDA 22-010 with no user fees.

In the original NDA, single and multiple dose pharmacokinetics and dose-proportionality of articaine and metabolite were characterized following the administration of Septocaine® —formulation. Waiver for bioavailability of Septocaine® — was granted since the two formulations are proportionally similar with respect to articaine with the only difference in the amount of epinephrine. Literature was submitted which included pharmacokinetics in pediatric population (4-18 years old).

In this submission, data from one pharmacokinetic study (ART-03-001) and three clinical studies were submitted in support of the approval of the new strength.

In study ART-03-001, the systemic exposure to articaine was compared following administration of Septocaine®— and Septocaine® —to induce intraoral maxillary infiltration and mandibular nerve block anesthesia in 14 healthy subjects in a croos over fashion. The maximum dose was selected to assess articaine plasma levels found with different concentrations of epinephrine. The total anesthetic volume used for the treatments was a dose of 11.9 mL (seven 1.7 mL dental cartridges) or 480 mg articaine HCl. The maximum recommended dose for 4% articaine 1:100,000 epinephrine is 7 mg/kg (3.2 mg/lb) of body weight. The articaine C_{max} and AUC were compared between the two Septocaine® groups. The geometic mean ratio (0.95) and the 90% confidence intervals (79.8 – 112%) suggest that the C_{max} is comparable in subjects receiving Septocaine® —and Septocaine® —— The time for the observed peak plasma concentrations was similar (0.37 hours) in the two groups. Therefore, from a systemic pharmacologic effects point of view, the two strengths will be expected to have similar profiles.

2 QBR

2.1 General Attributes

Originally, NDA 20-971 was a 505(b)(1) application submitted by this sponsor in March of 1998, where approval was sought for use of two Septocaine® products, Septocaine® — and Septocaine® —. The Agency approved only the higher epinephrine strength (1:100,000) 4% articaine HCl formulation (Septocaine® —) in 1998.

The current application is a resubmission of Septocaine® — (4% articaine HCl with 1:200,000 epinephrine) originally submitted for consideration in NDA 20-971. For administrative reasons, Agency split this application and assigned NDA number 22-010 to Septocaine® —. The original receipt date for NDA 22-010 is considered to be the same as that of NDA 20-971, that is March 30, 1998. This submission is considered a complete response to previously submitted NDA 20-971 (new assigned NDA 22-010).

2.2 General Clinical Pharmacology

2.1.1 Are the systemic articaine levels following administration of Septocaine® — and Septocaine® — similar?

The rate and extent of systemic absorption in terms of T_{max}, Cmax and AUC of articaine after the administration of Septocaine® — and Septocaine® — are similar and therefore both strengths are expected to have similar systemic pharmacologic effects.

In study ART-03-001, the systemic exposure to articaine was compared following administration of Septocaine® —and Septocaine® —to induce intraoral maxillary infiltration and mandibular nerve block anesthesia. The study was conducted in a double-blind, randomized, crossover design in 14 healthy subjects (13 male and 1 female) between the ages of 21 and 65 years and weighing between 150 and 200 pounds. The maximum dose was selected to assess articaine plasma levels found with different concentrations of epinephrine. The total anesthetic volume used for the treatments was a dose of 11.9 mL (seven 1.7 mL dental cartridges) or 480 mg articaine HCl. The maximum recommended dose for 4% articaine 1:100,000 epinephrine is 7 mg/kg (3.2 mg/lb) of body weight. The dose of study medications was chosen in accordance with

published local anesthetic recommendations for oral anesthetic injections. A topical anesthetic ( ) was applied to the mucosa prior to injection.

Injections were made slowly (about 1 mL/minute) with frequent aspirations in order to avoid intravascular injection. Study drug was not to be injected into an inflamed or infected area. Plasma samples were collected upto 2 hours post-dose and analyzed for articaine concentrations, employing a validated LC-MS-MS analytical method. Please refer to the attached study synopsis for additional details. Comparison of C_{max} and $AUC_{(0-2)}$. The articaine C_{max} and AUC calculated over the two hours of blood sampling were compared between the two Septocaine® groups. The geometic mean ratio (0.95) and the 90% confidence intervals (79.8 – 112%) suggest that the C_{max} is comparable in subjects receiving Septocaine® — and Septocaine® —. The time for the observed peak plasma concentrations was similar (0.37 hours) in the two groups. Plasma AUC was similar following administration of Septocaine® — and Septocaine® — (See table below). Please refer to the medical office review for safety assessment.

Table below compares C_{max} and $AUC_{(0-2)}$ of articaine in plasma following 11.9 mL (480 mg articaine HCl) dose of Septocaine® — and Septocaine® —.

Parameter	A200	A100	Ratio of Geom. Means (%)	90% Confidence Interval (%)	Intra-Subject CV (%)
	Geometric Mean Arithmetic Means (CV%)				
AUC_{0-t} (ng.h/mL)	1901.81 2012.54 (36)	1860.90 1988.54 (38)	97.85	83.77 – 114.30	21
AUC_{inf} (ng.h/mL)	2275.76 2440.44 (42)	2247.52 2478.72 (50)	98.76	84.78 – 115.04	21
Cmax (ng/mL)	2064.24 2145.00 (29)	1957.95 2036.67 (31)	94.85	79.77 – 112.78	24
Tmax (h)	0.37 (46)	0.36 (30)			
kel (1/h)	1.0022 (26)	1.0534 (30)			
Half-life (h)	0.74 (28)	0.73 (36)			

2.3 Intrinsic Factors and Extrinsic Factors

2.3.1 Does the pharmacokinetics of articaine change with intrinsic and extrinsic factors?

Articaine pharmacokinetics following Septocaine® — was reviewed in the original NDA 20-971. Since the pharmacokinetics of articaine from the two formulations is similar, the recommendations made previously in the package insert for special populations will be applicable to this product as well.

2.4 General Biopharmaceutics

2.4.1 What is the forumulation(s) composition?

The Septocaine® — and — products are solutions for injection. The difference between the two products in relation to articaine HCl is the strength of epinephrine, which is present in the ratio of 1:100,000 in Septocaine® —— or 1:200,000 in Septocaine® — . Epinephrine is a vasoconstrictor that in appropriate concentrations will serve to localize articaine at the site of application and slowing down the escape into systemic circulation. The formulation composition of Septocaine products is indicated below.

INGREDIENT	Septocaine —— (1:200,000 epinephrine)	Septocaine — (1:100,000 epinephrine)
Articaine hydrochloride	4.000 g	4.000 g
Epinephrine base	0.0005 g*	0.001 g*
Sodium metabisulphite	0.050g	0.050g
Sodium chloride	0.160 g	0.160 g
Sodium hydroxide solution q.s.		

2.5 Analytical

2.5.1 Is the analytical assay method adequately validated?

The plasma articaine levels were analyzed employing an adequately validated HPLC/MS/MS method. The summary of analytical method validation is presented in the appendix 4.2.

3 Labeling

Sponsor proposed labeling changes to existing Septocaine® — label are noted as bold font, and strike-through text for additions and deletions respectively. Reviewer's changes are noted as italics font and double-strike-through text for additions and deletions, respectively.

9 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_X_ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

4.2 PK Study ART-03-001 synopsis

SYNOPSIS

Protocol ART-03-001

Name of Company:	Novocol Pharmaceutical of Canada, Inc.
Name of the Finished Product:	Septocaine — ® [pending FDA approval]
Name of Active Ingredients:	articaine hydrochloride and epinephrine bitartrate
Title:	Peak plasma articaine concentrations and cardiovascular responses following intraoral administration of 4% articaine HCl with 1:200,000 epinephrine and 4% articaine HCl with 1:100,000 epinephrine
Investigators/Study Center:	[redacted]
Publications:	None
Study Period:	November 24, 2004 to February 16, 2005
Study Phase:	I [ ] II [ ] III [x]
Objective:	To determine the peak plasma articaine concentration and the cardiovascular responses of 4% articaine HCl with 1:200,000 epinephrine as compared to 4% articaine HCl with 1:100,000 epinephrine, following their administration for intraoral anesthesia
Methodology:	The study was a double blind, randomized, crossover study at one study site. The two anesthetic study medications (4% articaine HCl with 1:200,000 epinephrine and 4% articaine HCl with 1:100,000 epinephrine) were administered to induce intraoral maxillary infiltration and mandibular nerve block anesthesia. Each subject received both anesthetic formulations to determine articaine plasma concentration, time to peak plasma concentration, effect on cardiovascular parameters and subject descriptive rating of anesthesia.
Number of Subjects:	14 enrolled (13 male, 1 female), 13 completed

Subject Population:	Adults between 21 and 65 years of age weighing between 150 and 200 pounds.
Test Product:	4% articaine HCl with 1:200,000 epinephrine 7 dental cartridges (11.9 mL) with a total dose of 476 mg articaine hydrochloride; 0.0595 mg epinephrine base
Concurrent Control:	The currently marketed anesthetic formulation 4% articaine HCl with 1:100,000 epinephrine (40 mg articaine hydrochloride; 0.017 mg epinephrine base) serves as the clinical comparator for the test product (4% articaine HCl with 1:200,000 epinephrine).
Primary Efficacy Variables:	The primary outcome efficacy variable of interest is: 1. Peak plasma concentrations of articaine. Secondary outcomes of interest include: 1. Time to peak plasma concentrations of articaine. 2. Change in cardiovascular responses (heart rate, systolic blood pressure, diastolic blood pressure, mean blood pressure, stroke volume, estimated cardiac output, large artery elasticity index (C1), small artery elasticity index (C2), systemic vascular resistance) following anesthetic administration. 3. Subject rating of anesthetic efficacy.
Safety Evaluations:	Adverse events, vital signs, brief physical examination, cardiovascular parameters
Statistical Methods:	Descriptive statistics included number, mean, standard deviation, median, minimum and maximum. Statistical inferences made in this study include McNemar's test, paired t-tests, confidence intervals and PROC MIXED models with Tukey-Kramer adjusted multiple comparison tests.

SUMMARY - CONCLUSIONS

Results and Conclusions:

The results in this study confirmed the safety and efficacy of 4% articaine HCl with 1:200,000 epinephrine for use as a local dental anesthetic:

- There was no significant difference in the Cmax for the two formulations (2145 ng/mL for A200, 2037 ng/mL for A100).
- There was no significant difference in the Tmax for the two formulations (0.37 hours for A200, 0.36 hours for A100).

- The following differences were found in the cardiovascular parameters and vital signs between A200 and A100:
  - Heart rate at 10 minutes post-dose (A200: 69.6 bpm, A100: 78.2 bpm, p = 0.0471).
  - Systolic blood pressure at 10 minutes post-dose (A200: 124.8 mm Hg, A100: 130.6 mm Hg, p = 0.0456).
  - Small artery elasticity index at 70 minutes post-dose (A200: 11.4 mL/mm Hg, A100: 12.9 mL/mm Hg, p = 0.0357).
  - Cardiac output at 10 minutes post-dose (A200: 6.2 L/min, A100: 6.35 L/min, p = 0.0445) using Wilcoxon Signed Rank Test.
  - Maximum change in heart rate from pre-dose (A200: -3.1 ± 11.2 bpm, A100: 1.6 ± 17.6 bpm, p = 0.0288)
  - Time to maximum change of systemic vascular resistance index from pre-dose (A200: 74.6 ± 36.0 min, A100: 52.9 ± 38.7 min, p = 0.0249).
  - Pre-treatment systolic blood pressure (A200: 121.4 ± 7.7 mm Hg, A100: 127.2 ± 6.5 mm Hg, p = 0.0419).
- There were no significant differences in the success rate of anesthesia between the A100 and A200 treatments based on subject descriptive rating of anesthesia.
- Multiple doses (11.9 mL) of 4% articaine HCl with 1:200,000 epinephrine were safe and well tolerated with 5 subjects (35.7%) experiencing at total of 6 adverse events 5 of which were mild and 1 was of medium intensity with 2 considered probably treatment related.
- Multiple doses (11.9 mL) of 4% articaine HCl with 1:200,000 epinephrine were efficacious with 12 subjects experiencing complete anesthesia based on achieving a subject descriptive rating of 4 during the 120-minute visit.

4.3 Analytical Method validation report summary

1.0 SUMMARY

A liquid chromatographic tandem mass spectrometric method for the determination of Articaine in human plasma has been re-validated due to changes in sample preparation and extraction procedures, and cross-validated between human plasma with sodium heparin as anticoagulant, serum separator tube (SST) gel clot serum, and hemolyzed human plasma with sodium heparin as anticoagulant at [redacted] Division. Procaine was used as the internal standard. The method involved a liquid-liquid extraction and has demonstrated the following performance characteristics:

Matrix:	Human Plasma, Sodium Heparin (0.2 mL)	
	SST Gel Clot Serum (0.2 mL)	
Lower Limit of Quantitation:	5.00 ng/mL	
Concentration Range:	5.00 ng/mL – 1000 ng/mL	
Selectivity SST Gel Clot Serum:	No significant interference	
Concomitant Medication:	No significant interference	
Matrix Effect SST Gel Clot Serum:	Precision:	≤ 2.2 %
Recovery from Sodium Heparin Plasma:	Articaine:	86.7 % to 89.4%
	Procaine:	81.2 %
Recovery from SST Gel Clot Serum:	Articaine:	73.9 % to 89.4 %
	Procaine:	80.2 %
Within Batch Precision:	≤ 12.6.%	
Within Batch Accuracy:	87.1 % to 109.3 %	
Between Batch Precision:	≤ 6.0 %	
Between Batch Accuracy:	93.6% to 102.7 %	
Correlation Coefficient:	≥ 0.9974	
Stability:		
Freeze-Thaw SST Gel Clot Serum:	Three (3) cycles	
Short term: SST Gel Clot Serum:	5.00 hours in an ice bath (Bench Top)	
	24.75 hours at 5 ± 3°C (Refrigerated)	

Dilution Integrity:

SST Gel Clot Serum diluted with Sodium Heparin Human Plasma

% Difference: 13.4 %

Hemolyzed Human Plasma diluted with Sodium Heparin Human Plasma

% Difference: 1.2 %

4.4 CPB Filing Memo

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**22-010**	**Brand Name**	**Septocaine®**
OCPB Division (I, II, III)	**DCPB-2**	**Generic Name**	**Articaine 4% solution for injection**
Medical Division	**DAARP**	**Drug Class**	**Local Anesthetic**
OCPB Reviewer	**Srikanth C. Nallani, Ph.D.**	**Indication(s)**	**For infiltration or nerve block anesthesia for dentistry**
OCPB Team Leader	**Suresh Doddapaneni, Ph.D.**	**Dosage Form**	**Injectable**
		Dosing Regimen	**25-100 mg for infiltration; 20-136 mg for nerve block; 40-204 mg for oral surgery**
Date of Submission	**9/29/2005**	**Route of Administration**	**Intra oral**
Estimated Due Date of OCPB Review	**2/29/2006**	**Sponsor**	**Deproco, Inc.,**
PDUFA Due Date	**3/29/2006**	**Priority Classification**	**Standard**
Division Due Date	**3 /1/2006**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	1	1	
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				

hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	X			
Total Number of Studies		1	1	

Filability and QBR comments

	"X" if yes	Comments
Application filable ?		Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?		Comments have been sent to firm (or attachment included) FDA letter date if applicable
QBR questions (key issues to be considered)	**Are the systemic articaine levels following administration of Septocaine® — and Septocaine® — similar?**	
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		