CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-010

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	New Drug Application
Submission Number	22-010 (N-000)
Letter Date	09/29/05
Stamp Date	09/30/05
PDUFA Goal Date	03/30/05
Reviewer Name	Jane Filie, M.D.
Review Completion Date	03/20/06
Established Name	Articaine Hydrochloride 4% with Epinephrine 1:200,000
Proposed Trade Name	Septocaine
Therapeutic Class	Dental anesthetic
Applicant	Deproco, Inc.
Priority Designation	Standard
Formulation	Solution for injection
Dosing Regimen	Single dose
Indication	Local, infiltrative or conductive anesthesia in simple and complex dental procedures
Intended Population	Adults and children 4 years and older

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

I recommend this NDA be approved.

This product was initially submitted for approval as part of NDA 20-971 in 1998 and found to be approvable provided the Sponsor:

- demonstrate Septocaine — is not inferior to the currently approved formulation
- characterize the anesthetic properties of Septocaine —
- demonstrate a difference between the two drug products
- demonstrate that there are no major safety concerns with the use of Septocaine —

The Sponsor satisfied each of the above items. Specifically, in two controlled trials, non-inferiority of the articaine formulation with epinephrine 1:200,000 to the articaine formulation with epinephrine 1:100,00 was demonstrated, and the Sponsor succeeded to demonstrate that one of the two formulations produces better hemostasis, and consequently, better visualization of the surgical field.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

This product has minimal to no abuse potential. Furthermore, it is likely that the use of this product would be limited to healthcare facilities and dental offices. Therefore, risk management activity was not required as part of the development plan for this drug product.

1.2.2 Required Phase 4 Commitments

None are required.

1.2.3 Other Phase 4 Requests

This application does not trigger the Pediatric Research Equity Act; however, the Sponsor will be encouraged to submit a Pediatric Proposal Study Request (PPSR).

Future trials should include monitoring of adverse events, in particular, unexpectedly prolonged anesthesia and changes in taste and sensation.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

This is the second cycle for the drug 4% articaine with epinephrine 1:200,000-Septocaine —. It was submitted in 1998 with its approved counterpart Septocaine®, which has 4% articaine with epinephrine 1:100,000.

Septocaine — is a local anesthetic of the amide class used for submucosal injection and is intended for use in clinical dentistry.

The Sponsor submitted a clinical program which consisted of three efficacy trials and a pharmacokinetic (PK) study. A total of 182 individuals participated in the studies and were exposed to doses of study drug ranging from 1.0ml to 11.9ml.

Study ART 02-001 assessed the anesthetic characteristics of 4% articaine with 1:200,000 epinephrine, and compared those with 4% articaine with 1:100,000 epinephrine and 4% articaine without epinephrine. Sixty-three subjects participated and were evaluated with an electric pulp tester (EPT), after administration of 1.7ml of study drug for inferior mandibular block.

Study ART 02-002 had the same study design as ART02-002. Sixty-three subjects were also enrolled and were evaluated with an EPT, after administration of 1.0ml of study drug for maxillary infiltration.

Study ART 02-003 assessed the hemostasis of the 4% articaine formulations with epinephrine by studying 42 patients that were subjected to bilateral oral surgery, during which they were exposed to doses ranging from 1.0 to 6.8ml.

Study ART 03-001 was a PK study where 14 subjects were exposed to 11.9 ml of both formulations of articaine and the Sponsor compared the pharmacokinetic profile of the two.

1.3.2 Efficacy

In Study ART 02-001, the efficacy rate was determined as the number of subjects who achieved complete anesthesia within 10 minutes, after injection of 1.7ml of study drug for inferior mandibular block. Complete anesthesia was determined by achieving a level of 80 using an electric pulp tester. The overall efficacy rate was low: only 42.8% of the subjects achieved an EPT value of 80 within 10 minutes. The efficacy varied significantly among the study centers: 68.6% for the University of Pittsburgh, 39.7%, for the University of Pennsylvania and 19.7% for The Forsythe Institute.

Nevertheless, since each individual served as its own control, the analysis by treatment arm demonstrated that the formulation with 1:200,000 epinephrine was not inferior to the formulation with 1:100,000 epinephrine for inferior mandibular block. The time to onset and time of duration was similar for both formulations.

Study ART 02-002 had a similar study design, except that the subjects received 1.0 ml of the study drug for maxillary infiltration block. The overall efficacy rate was 88.2% and the success rates were more consistent across the sites: University of Pennsylvania 90.2%, University of Pittsburgh 88.9% and The Forsythe Institute 85.7%. The analysis of the success rate by treatment arm demonstrated that the formulation with 1:200,000 epinephrine is not inferior to the formulation with 1:100,000 epinephrine for maxillary infiltration. The time to onset and time of duration was similar for both formulations.

Study ART 02-003 intended to demonstrate a difference in hemostasis between both drugs. In the absence of validated methods for describing visualization of the surgical field and quantifying blood loss during surgical procedures the Sponsor chose to apply rating systems to obtain the surgeons' impressions of clarity of the surgical fields and of the amount of bleeding during surgical procedures. The Sponsor also attempted to measure the volumes of blood loss during surgical procedures using both articaine products with epinephrine. The range of volumes collected varied across the centers with a wide variation in mean volumes: the University of Pittsburgh had the largest volumes collected, and The Forsythe Institute the least. There were negative values recorded which indicates the collection process was difficult (patients swallowed some of the fluid). However, when comparing the volumes of blood loss by treatment arm in each center, there is a trend which indicates that there was less blood loss with the formulation containing 1:100,000 epinephrine.

The analysis of the data resulting from the surgeons' rating of Visualization of the Surgical Field, the Sponsor was successful in demonstrating a difference in visualization between the two products. This reviewer's conclusion is that the surgical field was considered clear in 61.9% of the surgeries with the 1:100,000 formulation and in 47.6% of the surgeries with the 1:200,000 formulation.

The PK study, ART03-001, demonstrated that the lower dose of epinephrine has minor impact in the systemic levels of articaine and the two formulations have a similar PK profile.

I concluded that 4% articaine with epinephrine 1:200,000 was not inferior to 4% articaine with epinephrine 1:100,000 in terms of analgesic efficacy, and the use of the formulation 4% articaine with epinephrine 1:100,00 can be recommended when better visualization is required.

1.3.3 Safety

There were 182 patients enrolled in the four studies conducted. The doses to which the subjects and patients were exposed ranged from 1.0 to 11.9 ml, at single applications.

There were no deaths and no serious adverse events. All adverse events were of mild to moderate intensity and all were resolved by the end of the studies.

There were no unexpected adverse events given what is known about articaine from the previously approved NDA for articaine with 1:100,000 epinephrine and from the worldwide post-marketing experience.

There were a total of 113 adverse events reported in all studies combined, for 485 exposures to articaine (includes all formulations with and without epinephrine). There were 52 adverse events reported for 4% articaine with 1:100,000 epinephrine, 40 adverse events for 4% articaine with 1:200,000 epinephrine and 21 adverse events for 4% articaine alone. The most common adverse events that occurred at an incidence > 1% were pain, headache, positive blood aspiration into syringe, swelling, trismus, nausea and emesis, sleepiness, numbness and tingling, palpitation, ear symptoms (earache, otitis media), and cough. Sleepiness and palpitations were only detected in the study where subjects received the maximum recommended dose.

There is evidence of a direct relation between higher doses of anesthetic and increased adverse event rate.

The participants in the studies were generally healthy adults, and the studies excluded pediatric and geriatric patients.

This drug is intended for use in dental offices and healthcare facilities; therefore, there is no potential for abuse of this drug.

There are reports of paresthesias in the post-marketing adverse event report submitted by the Sponsor and in AERS.

1.3.4 Dosing Regimen and Administration

The Sponsor suggests that the dosing recommendations remain the same as the currently approved label. The current labeling recommendations are based on studies using only 4% articaine with epinephrine 1:100,000. The current studies showed efficacy with doses up to 6.8ml (4 cartridges) of both formulations and explored pharmacokinetics up to 11.9ml.

1.3.5 Drug-Drug Interactions

It is known that administration of local anesthetics containing epinephrine or norepinephrine to patients receiving monoamine oxidase inhibitors or tricyclic antidepressants may produce severe prolonged hypertension. Phenothiazines and butyrophenones may reduce or reverse the pressor effect of epinephrine, which may shorten the duration of analgesia. Concurrent use of these agents should generally be avoided. In situations when concurrent therapy is necessary, careful patient monitoring is essential.

No studies of drug-drug interaction potential were performed for this application.

1.3.6 Special Populations

The use of Septocaine — was not assessed in the pediatric and geriatric population in this clinical program. The currently approved product has pediatric and geriatric labeling that was derived from studies of the original NDA 20-971 using the formulation with 1:100,000 epinephrine.

The label of the approved formulation indicates that there are no well controlled studies in pregnant women and it is not known whether articaine is excreted in human milk.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Septocaine is a new combination product which contains 4% articaine hydrochloride with 1:200,000 epinephrine. It is a local anesthetic of the amide class for submucosal injection and it is intended for use in clinical dentistry. The Sponsor proposes the name Septocaine , in resemblance to its other approved formulation Septocaine®, which contains 4% articaine HCl and 1:100,000 epinephrine. The Sponsor proposes changing the name for the currently approved product to Septocaine .

The currently marketed Septocaine® is indicated for local, infiltrative, or conductive anesthesia in both simple and complex dental and periodontal procedures. The Sponsor seeks to make a distinction between the two drug products by claiming that "Septocaine®

contained in Septocaine® . Septocaine® during operative or surgical procedures to improve visualization of the surgical field."

The proposed dosing regimen is the following (from the Sponsor's proposed label):

DOSAGE AND ADMINISTRATION

Table ~~3~~-2 (Recommended Dosages) summarizes the recommended volumes and concentrations of Septocaine® for various types of anesthetic procedures. The dosages suggested in this table are for normal healthy adults, administered by submucosal infiltration and/or nerve block.

Table 32. Recommended Dosages

Procedure	Septocaine® Injection	
	Volume (mL)	Total dose of articaine HCl (mg)
Infiltration	0.5 – 2.5	20 – 100
Nerve block	0.5 – 3.4	20 – 136
Oral surgery	1.0 – 5.1	40 – 204
THE ABOVE SUGGESTED VOLUMES SERVE ONLY AS A GUIDE. OTHER VOLUMES MAY BE USED PROVIDED THE TOTAL MAXIMUM RECOMMENDED DOES IS NOT EXCEEDED.		

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

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

MAXIMUM RECOMMENDED DOSAGES

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

Pediatric Patients: Use in pediatric patients under 4 years of age is not recommended. The quantity to be injected should be determined by the age and weight of the child and the magnitude of the operation. Do not exceed the equivalent of 7 mg/kg (0.175 mL/kg) or 3.2 mg/lb (0.0795 mL/lb) of body weight.

The recommendations above had been made based on studies using the articaine formulation with 1:100,000 epinephrine.

Articaine is widely used in Europe for dental procedures and is available as Ultracaine® (articaine 5%).

2.2 Currently Available Treatment for Indications

There are other local anesthetics approved for dental use:

- 2% lidocaine HCl; 1:100,000-1:50,000 epinephrine
- 2% mepivacaine HCl; 1:20,000 levonordefin
- 3% mepivacaine
- 4% prilocaine
- 4% prilocaine; 1:200,000 epinephrine
- 0.5% bupivacaine; 1:200,000 epinephrine
- 1.5% etidocaine; 1:200,000 epinephrine*
- 4% articaine 1:100,000 epinephrine

*withdrawn from the market but not due to safety reasons

2.3 Availability of Proposed Active Ingredient in the United States

Septocaine® is manufactured in Canada by Novocol Pharmaceutical of Canada, Inc., and distributed by Septodont, Incorporated, New Castle, Delaware, USA.

2.4 Important Issues With Pharmacologically Related Products

The more important issues regarding the use of local anesthetics and vasoconstrictors are those involving safety and are generally related to systemic exposure. With local anesthetics, the issues include the following.

- Central nervous system reactions that range from CNS excitation with light-headedness, dizziness, paresthesias and acute anxiety at lower plasma levels, to generalized tonic-clonic seizure activity, depression of conscious activity and respiratory arrest with profound depression of the medullary respiratory center at higher plasma concentrations.
- Cardiac reactions including dose-dependent depression of myocyte activity with decreases in myocardial contractility beginning at doses that achieve sodium channel blockade. Life-threatening arrhythmias and cardiovascular collapse can occur at higher systemic exposures. Cardiac toxicity is related, in large part, to agent-specific kinetics of sodium channel block.
- Allergic-type responses to local anesthetics range from contact hypersensitivity to anaphylactoid and anaphylactic reactions. The preservatives, methylparaben and metabisulfite, commonly used in multidose preparations may, independently of the local anesthetic, significantly increase the likelihood of an allergic-type response. Para-aminobenzoic acid (PABA), a metabolite of the ester local anesthetics, is commonly found in the environment and therefore, may serve as a significant source of allergic reactions as many patients present already sensitized to this compound.

Issues associated with vasoconstrictive agents include the following responses to topical and systemic exposures.

- Decreased blood flow in tissues surrounding the site of locally administered vasoconstrictive agents may lead to ischemia and necrosis.
- Vascular uptake of adrenergic agents can lead to plasma levels sufficient to result in tachycardia, hypertension, flushing, arrhythmia, myocardial ischemia, and possibly, myocardial infarction.

Combining a relatively short-acting local anesthetic with a vasoconstrictor may enhance the quality and duration of the block, and reduce the amount of local anesthetic required for a particular procedure. On the negative side, if the block significantly outlasts the procedure, it may pose a safety risk in that the patient may be unaware of trauma or injury to the anesthetized area, or of problems related to the block or procedure, such as nerve injury, that may be delayed in being diagnosed and/or treated.

2.5 Presubmission Regulatory Activity

The original IND for Septocaine was submitted on October 18, 1996 and was assigned the IND number 51-721.

According to the Sponsor, during a pre-IND meeting on May 10, 1998 and a meeting dated January 10, 1997, it was agreed between the Sponsor and the FDA that the NDA could cover both drug products and in addition to phase 3 studies on Septocaine —, a pharmacokinetic/ efficacy study using Septocaine — would be adequate to approve the two products.

The Sponsor submitted the original NDA 20-971 on March 30, 1998 for two drug formulations: 4% articaine HCl with 1:100,000 epinephrine (referred to then as Septanest —) and 4% articaine HCl with 1:200,000 epinephrine (referred then as Septanest —). In a teleconference held on December 3, 1998, the Sponsor agreed to modify the proposed name "Septanest —" because the acronym "'—'" suggested that the product was for ——— The nomenclature proposed by the Sponsor became Septanest — for the formulation containing 1:200,000 epinephrine and Septanest — for the formulation with 1:100,000 epinephrine. This name was again rejected and ultimately the name Septocaine was proposed, which the Agency found acceptable.

In January 1999, the Agency issued an Approvable letter for both formulations. The requirements for approval were the resolution of two CMC deficiencies (satisfactory approval of the manufacturing facilities and satisfactory resolution of the packaging deficiencies) as well as the acceptance of the final printed label. A complete response was received on May 4, 1999 and because of a failed manufacturing site inspection, a second approvable letter was sent on May 5, 1999, requesting correction of CMC and labeling issues.

On March 16, 2000, a teleconference was held to discuss labeling changes and to request additional information regarding the NDA. The Agency requested that the Sponsor submitted a justification for the need of the formulation containing 1:200,000 epinephrine. After re-reviewing the studies that were submitted, the Agency questioned the need for the formulation with 1:200,000 epinephrine, since all the clinical data were based on the formulation with 1:100,000 epinephrine. Upon review of the final labeling it was felt that there was insufficient data describing the formulation with the lower concentration of epinephrine. Consequently, the Division decided it was not possible to craft a label with specific instructions for appropriate selection between the two formulations. According to the Medical Officer Review of NDA 20-971, p.10 : "A dose of 4% articaine hydrochloride with 1:100,000 epinephrine was chosen for the phase 3 clinical trials, since it might be expected that more adverse events would be reported with the higher dose of epinephrine compared to the lower dose. The FDA agreed that it was unnecessary to independently test 4% articaine hydrochloride with 1:200,000 epinephrine, or to test the efficacy of epinephrine. Lidocaine was taken as the standard against which to compare articaine; adverse event rates with lidocaine were to be compared to adverse event rates with articaine at follow-up. Due to this comparison, a ratio of 2:1 articaine (1000): lidocaine (500) patients were to be enrolled. This was also agreed upon by the FDA".

The proposed solution was to approve the 4% articaine with 1:100,000 formulation with directions for use. If the Sponsor wished to market the other formulation, an efficacy supplement could be approved at a later time, if a meaningful clinical difference could be found in a direct head-to-head comparison, providing a basis for selection between the two formulations.

An Approval Letter for Septocaine was issued on April 3, 2000, after manufacturing inspections, CMC and labeling issues were fully addressed. In regards to the fulfillment of the pediatric study requirements the letter stated:

"Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 FR 66632). We note that you have fulfilled the pediatric study requirement at this time for children aged 4 or older. We are waiving the pediatric study requirement for children less than 4 years old for this action on this application."

On September 30, 2005 the Agency received this NDA supplement. Because this was a re-submission of a product strength submitted in the original NDA submission, this application was split for administrative purposes and was assigned another NDA number, now NDA 22-010. The original receipt date for NDA 22-010 is to be considered to be the same as that of NDA 20-971, which is March 30, 1998. The Agency deferred the submission of pediatric studies until December 31, 2008 and requested the submission of the pediatric drug development plan within 120 days from the date of the notification (November 23,2005). The Sponsor's response to this deferral will be discussed in the Section 8.4. Pediatrics.

Since approval there were communications with the Sponsor to discuss the requirement for approval of the second formulation of articaine (meeting June 25, 2002, and teleconferences on April 30, and August 28, 2003).

From the meeting minutes dated June 25, 2002: The Sponsor was informed that the studies would need to demonstrate how the second product worked and that it was safe; a comparator would be useful for characterization only. Instead of using prilocaine 4% with epinephrine 1:200,000 as an active control, a better choice would be to study the two articaine formulations against each other. The required data for articaine 4% with epinephrine were the drug's clinical parameters: onset of effect, duration of effect, anesthesia depth, infiltrative technique and /or sites. The patient population enrolled in the study could resemble the patient population studied in the original NDA. The purpose of the comparator arm would be to identify the background phenomena, not to seek superiority. Studies on cardiovascular compromised patients were considered unnecessary, and inappropriate. One three-arm study – articaine 4% with epinephrine 1:200,000, articaine 4% with epinephrine 1:100,000 and articaine alone- was required. The study should have appropriate endpoints and adequate size.

It was stated that demonstration of a clearer fields (better hemostasis) would be one way of distinguishing on product from the other. The Sponsor needed to characterize the new formulation and if it was demonstrated that they were the same, the Sponsor would need to

demonstrate that the formulation was at least as safe as the approved product. The Agency suggested that the Sponsor could consider a PK/PD, animal, or bioavailability study for cardiovascular parameters or a PK/PD study with both formulations in humans. The Sponsor inquired if it would be sufficient to characterize the product as requested and demonstrate a difference in hemostasis. This was considered acceptable by the Agency.

At a teleconference on April 30, 2003, the Division discussed with the Sponsor the adequacy of their four proposed protocols. The key points of the teleconference were:

- The number of patients in the program seemed adequate.
- The Division asked for the clinical safety database, that about 12 patients be studied at the maximum recommended dose and a comparison of the local anesthetic absorption of the two formulations.
- The Sponsor should consider vital signs monitoring as a marker for epinephrine symptoms and plasma articaine levels. It was indicated to the Sponsor that of one these studies would be acceptable.
- The Sponsor should incorporate anesthesia efficacy endpoints into the periodontal study (onset, duration and scoring of symptoms).
- It was deemed acceptable to the Division that a 2-arm kinetic study was employed instead of a 3-arm study like the efficacy studies.

At a teleconference on August 28, 2003, there was further discussion about the proposed studies. The key points of the teleconference were:

- Studies ART02-001 and 002 would be more appropriately powered as non-inferiority trials.
- The Sponsor was informed that the studies might not be able to measure differences between the two formulations, but if the product seemed safe and that efficacy could be demonstrated, the Division would consider approval of the second formulation.
- Local neurotoxicity was addressed. The Sponsor and the Agency indicated that both would be monitoring this matter. No specific safety measures for neurotoxicity monitoring were discussed.

Since then there have been no other discussions with the Sponsor in regards to the development plan.

In August 2005, the Sponsor submitted a labeling supplement proposing a change in the name to ——. The Office of Drug Safety was consulted and the change was considered acceptable with modifications to the product labeling that were suggested.

During this NDA a consult to the Division of Medication Error and Technical Support (DMETS) was requested to assess the adequacy of the proprietary names Septocaine — and Septocaine —. DMETS considered the names inadequate because these are combination products and the modifier does not indicate which ingredient it is modifying (whether it is articaine or epinephrine) and it does not accurately define the concentration of the product which it describes (epinephrine). For further details, refer to the consult dated February 21, 2006.

2.6 Other Relevant Background Information

Despite the fact that another NDA number was issued, the Sponsor has been exempted from a User Fee for this NDA application. In March 1998, the Sponsor submitted an NDA for Septocaine — and Septocaine — and paid the application fee associated with the NDA. The Agency accepted the application for filing, but the application, as it related to Septocaine —, was not approved, neither was it withdrawn.

Upon filing, deficiencies were noticed:

- Financial disclosure documentation for investigators was missing.
- Indexing of the volumes was inadequate.
- The Integrated Summary of Safety presented data individualized by study, but did not include safety data compiled from all studies into a single comprehensive table.

This drug product is approved in foreign countries. The Sponsor submitted the foreign labels too late in the cycle for inclusion in this review.

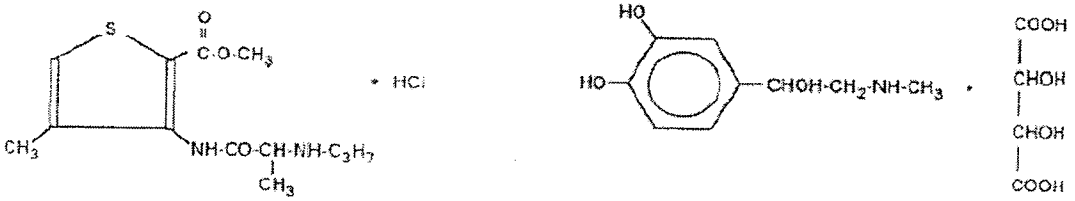
3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC

Articaine is a short-acting local anesthetic of the amide type. The structure of articaine is similar to other amide local anesthetics, except that it contains an ——— The rapid breakdown of articaine leads to a low level of systemic toxicity. Articaine is better able to diffuse through soft tissues and bone than other local anesthetics.

Articaine is chemically 4-methyl-3-[2-(propylamino)-propionamido]-2-thiophene-carboxylic acid, methyl ester hydrochloride (a racemic mixture) with a molecular weight of 320.84. Epinephrine bitartrate is chemically (-)-I-(3, 4-dihydroxyphenyl)-2-methylaminoethanol (+) tartrate (1:1 salt) with a molecular weight of 333.3. The structures of articaine and epinephrine are shown below.

ARTICAINE **EPINEPHRINE**



Septocaine® is a sterile aqueous solution for use in dental anesthesia. It contains two active ingredients, articaine hydrochloride and epinephrine bitartrate. A new formulation is proposed, in which the 4% articaine hydrochloride is combined with epinephrine at the strength of 1:200,000 instead of 1:100,000. The two products are otherwise the same.

Septocaine® — is packaged in single-use cartridges for use in a standard dental syringe. Each cartridge contains 1.7 ml of solution.

Articaine is manufactured by [redacted]. The manufacturing process is described in Drug Master Files (DMF) — and DMF —; respectively. The specifications for articaine hydrochloride include [redacted]

The vasoconstrictor epinephrine is included in the formulation as the bitartrate salt. This ingredient is manufactured by [redacted] and the process is described in DMF — . The specifications conform to the requirements of the current USP monograph.

The sponsor intends to manufacture the new product at Novocol Pharmaceutical of Canada, Inc., an affiliate of the sponsor in Cambridge, Ontario, Canada, using [redacted] processing. Additional inactive ingredients in the formulation are sodium chloride, sodium metabisulphite and sodium hydroxide. The ingredient sodium metabisulphite is used as a [redacted] The product specifications include identification tests for each active ingredient, pH, assay of each active ingredient and sodium metabisulphite, mean volume, [redacted], particulate matter, sterility and [redacted]

Stability studies have been performed for the finished drug product, packaged as proposed for commercial use. Epinephrine has a known susceptibility to oxidation, which has been considered in development of the formulation for the product. Stability studies of the drug product show that the epinephrine and the sodium metabisulphite contents slowly decrease with time.

As of the time of this review, the chemistry reviewer is awaiting additional data that was requested from the Sponsor, and the review has not been completed. For further details refer to the chemistry review.

3.2 Animal Pharmacology/Toxicology

The animal pharmacology and toxicology was previously addressed in the original NDA 20-971. From the Clinical Review of the original NDA, p.7:

"The preclinical data came primarily from three sources:
(1) toxicity studies using subcutaneous administration of Septanest -five acute toxicity [three with epinephrine and two without epinephrine], three repeat-dose toxicity [two with epinephrine, one without epinephrine], one skin sensitivity [without epinephrine] and six repeat-dose studies [with epinephrine] with local tolerance components, seven reproductive studies [four with epinephrine, three without epinephrine], five mutagenicity [one with epinephrine, four without epinephrine], and two toxicokinetic studies (with epinephrine) following single and repeat dosing;
(2) representative publications with other formulations of articaine; and
(3) one multifaceted pharmacology/toxicology study with the Hoechst formulation of articaine with and without epinephrine.

It was concluded that Septanest with epinephrine has a mechanism of action and toxicity profile similar to that of other amide-type local anesthetics. In studies with the mouse, rat and dog, the no-observed effect level (NOEL) of a single dose of subcutaneously administered Septanest with 1:100,000 epinephrine ranged from 3-fold to 10-fold greater than the maximum recommended dose in man (7 mg/kg). The C_{max} of Septanest with 1:100,000 epinephrine at the NOEL dose in rats and dogs was 2- to 3-times greater than the C_{max} of approximately 900 ng/ml found following administration of 204 mg (5.1 ml, 3 vials Septanest) articaine with 1:200,000 epinephrine to adults (equivalent to a dose of 2.9 mg/kg in adults with a mean weight of 70.7 kg). It was also 5- to 7-times greater than the C_{max} of approximately 400 ng/ml following a single dose of 68 mg (1.7 ml, 1 vial Septanest) articaine with 1:200,000 epinephrine (equivalent to a dose of 0.96 mg/kg in adults with a mean weight of 70.7 mg/kg). [Item 5.2, Vol. 1.3, pp. 19,22]"

The Sponsor presented more recent data in this submission. Paraphrased from NDA Vol. 28, p. 193-194: "Articaine with epinephrine 1:100,000 was shown to be safe following daily subcutaneous doses of 25mg/kg/day for 28 days in rats and dogs. A toxicity study indicated that daily subcutaneous injection of rats with articaine (25, 50 or 100mg/kg/day) with epinephrine 1:100,000 resulted in hematomas with skin ulceration and other localized tissue damage at the injection site. Deaths occurred in groups receiving 50 and 100mg/kg/day with no behavioral changes prior to death. A similar study in dogs resulted in hematomas and other tissue damage at the injection site, and behavioral changes at 80mg/kg/day, but no deaths.

Articaine showed no potential for mutagenic activity in both *in vitro* and *in vivo* assays.

Fertility, embryotoxicity and developmental studies in the rat and the rabbit, using subcutaneous injections of articaine (20, 40 and 80 mg/kg/day) with epinephrine 1:100,000 showed no effect on a variety of reproduction parameters, including incidence of live births and body weight at birth. Once again, no teratogenic effects were observed, and pups from treated mothers developed normally. Similar results were obtained using articaine without epinephrine".

For further detail, please refer to the pharmacology/toxicology review for this submission.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

Sources utilized for this review include:

- supplemental NDA package submitted by the Sponsor containing four phase 3 studies;
- original NDA 20-971;
- various correspondence and minutes of interactions with the Sponsor;
- consult requested to the Division of Dermatological and Dental Drug Products;
- consults requested to the Office of Drug Safety;
- search in the Adverse Event Reporting System (AERS);
- search in MedWatch;
- search in PubMed.

4.2 Tables of Clinical Studies

The table below summarizes the human trials conducted in support of this supplemental NDA application.

Table 4.2-1 **Table of Clinical Studies**

Type of Study	Study Number	Phase	Description
Efficacy and safety	ART02-001	3	These two studies had similar design with the main objective of demonstrating non- inferiority of the formulation containing epinephrine 1:200,000 compared to the approved formulation with epinephrine 1:100,000. Each had 63 healthy subjects. ART02-001 evaluated the efficacy of 1.7ml of study drug for inferior mandibular block; ART02-002 evaluated the efficacy of 1.0ml for infiltration anesthesia.
Efficacy and safety	ART02-002	3	
Efficacy an safety	ART02-003	3	The main objective of this study was the comparison of visualization of the surgical field following injection of each study drug for periodontal surgery in 42 patients.
Pharmacokinetic and safety	ART03-001	3	The main objective of this study was to compare the peak plasma concentration of articaine following injections up to the maximum dose of articaine (11.9ml). Thirteen subjects completed the study.

4.3 Review Strategy

Data from the four phase 3 trials were reviewed in detail. The safety review consisted of a review of the safety data from each trial individually, since the Sponsor did not provide an Integrated Summary of Safety (ISS) of all studies. This reviewer accommodated this deficiency by integrating the databases available. The Sponsor provided an integrated summary of the two efficacy studies ART02-001 and ART 02-002, and individual safety reports from the other two studies. The Sponsor has been asked to create a table merging all the safety information, which is pending at the time of this review. The Sponsor provided literature references in support of safety and efficacy and these will be discussed in the appropriate sections.

4.4 Data Quality and Integrity

It was noticed that there was a discrepancy in the anesthetic success rate across the study sites in Study ART 02-001. The success rate correlated with the financial compensation received by the Primary Investigators. This correlation however, did not occur in the other two efficacy studies. There is literature describing the variability in anesthetic success when using inferior mandibular block, which was the technique used in study ART 02-001 and there is enough evidence to support efficacy even without one of the studies.

Given the lack of correlation between the financial compensation and the results in the other efficacy studies, there is no reason to believe that there was a breech in the quality and integrity of the data. An investigation by the Division of Scientific Investigation (DSI) was triggered because of the financial compensation given to the study sites as indicated in the financial disclosure. As of the time of this review, according to a preliminary report from DSI, no irregularities have been encountered.

4.5 Compliance with Good Clinical Practices

The Sponsor has asserted that studies ART 02-001, ART 02-002, ART 02-003 and ART 03-001 were conducted in accordance with the ethical principles originating from the Declaration of Helsinki and in compliance with informed consent regulations 21 CFR Part 50 and institutional review board regulations 21 CFR Part 56, The Sponsor and clinical study sites also complied with International Conference on Harmonization (ICH) Part E6: Good Clinical Practice (NDA Vol. 28, p. 194).

4.6 Financial Disclosures

In compliance with 21CFR §54.4, Certification and Disclosure Requirements, the Sponsor submitted certification on the financial interest and arrangements of the clinical investigators who enrolled subjects into the clinical studies of Septocaine 200. This data was submitted late in the review process (stamp date: January 26, 2006).

Based on the information provided, there was substantial financial compensation in the form of honoraria and consulting fees to the primary clinical investigators which could have impacted the integrity of the studies. The financial arrangements were as follows:

- [redacted]: $120,163 in honoraria and consulting fees;

- [redacted]: $55,328 in honoraria and $24,500 in study equipment ([redacted]);
- [redacted]: $45,195 in honoraria.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

No pharmacokinetic data had been submitted using the articaine product with higher strength epinephrine (1:100,000) in the original NDA. It was felt that the articaine plasma concentrations achieved with the formulation containing epinephrine 1:200,000 were likely to be higher. The formulation with a lower concentration of epinephrine allows for more of the anesthetic to reach the systemic circulation, than a formulation containing a higher concentration of epinephrine. Therefore, the product evaluated then was to provide the most information regarding systemic toxicity for articaine.

The following is excerpted from page 4 of the Clinical Pharmacology and Biopharmaceutics Review of NDA 20971:

"The summary of pharmacokinetics of articaine and its metabolite articainic acid are provided here:

a. ABSORPTION: Following maxillary infiltration of two doses of 1.7 ml and 5.1 ml of Septanest — (4% articaine/1:200,000 epinephrine) in healthy volunteers, articaine was absorbed rapidly. The mean T_{max} across the dose range was 0.4 and 0.8 hours. Mean C_{max} of articaine and its major metabolite articainic acid following the 68 mg dose was 385 ng/ml and 1429 ng/ml and that following the 204 mg dose was 899 ng/ml and 3793 ng/ml. Mean $AUC_{0-\infty}$ of articaine and its major metabolite articainic acid following the 68 mg dose was 631 ng.hr/ml and 3751ng.hr/ml and that following the 204 mg dose was 1542 ng.hr/ml and 11,543 ng.hr/ml. This data indicates that there is dose proportionality in the pharmacokinetics of articaine and articainic acid, although data from at least 3 doses is necessary to accurately make this statement. Epinephrine PK were not evaluated in this NDA. However, considering the low doses of epinephrine administered, only low concentrations of epinephrine are likely to occur which may be undetectable.

b. DISTRIBUTION: The volume of distribution is about 4.5 L/kg for articaine and 0.6 L/kg for articainic acid (assuming complete conversion of articaine to articainic acid).

Plasma protein binding: In vitro protein binding studies indicate that articaine is about 80% bound to albumin with minor binding to δ-globulin.

c. ELIMINATION (METABOLISM AND EXCRETION):
Terminal phase half-life: Half-life of articaine is approximately 1.6 to 1.8 hours in healthy volunteers. Elimination half-life of articainic acid is similar to articaine. Mean Cl/F was found to be about 2000 ml/min for articaine.

Metabolism: Articaine is rapidly and extensively metabolized to articainic acid, possibly by plasma carboxyesterases (see the structures below for articaine and articainic acid). In order to stabilize these moieties in plasma, an esterase inhibitor, sodium or potassium fluoride was necessary.

In vitro metabolism studies in human lymphoblastoid systems containing specific CYP isozymes indicate that in vitro metabolism via CYP isozymes constitutes about 5 to 10% of the metabolism of articaine and is a minor metabolic pathway. This metabolism, however, indicates that articainic acid is the primary metabolite formed in liver microsomes.

Excretion: No mass balance study has been conducted with Septanest. However, literature data indicates that about 90% of radioactivity (of articaine dose) is excreted in urine after I.V. administration. Data from this NDA indicates that about 50% of the articaine dose is excreted in urine (mostly as articainic acid) within 24 hours. Only about 2% of the dose is excreted as unchanged articaine in urine. Literature also indicates that articainic acid glucuronide is one of the metabolites excreted in urine. Renal clearance of articaine was found to be 36.3 ml/min after the 68 mg dose and 50.2 ml/min after the 204 mg dose; and that of articainic acid was 175.6ml/min after the 68 mg dose and 160.6 ml/min after the 204 mg dose.

Age: The pharmacokinetics of articaine were not evaluated in elderly patients. A literature article was submitted to evaluate the PK of articaine in children of age 3 to 12 years old. Peak levels achieved, according to the sponsor, were comparable to the data obtained in adults (children dosed after adjustment for body weight). However, this data was obtained using a different formulation of articaine and the study itself was not designed appropriately to characterize the articaine pharmacokinetics in children. Hence, this data is insufficient to utilize it for labeling purposes.

Gender: The single and multiple dose PK study conducted in this NDA was carried out in both males and females. Analysis of the PK data for articaine and articainic acid in males and females indicated no statistically significant differences in any parameters except the renal clearance after the 68 mg dose. Renal clearance in males was found to be 28.3 ml/min and that in females was found to be 45.2 ml/min. Since such a difference was not reflected in the plasma concentrations and since renal elimination of unchanged articaine is only a minor pathway, this difference may not be clinically significant. However, this trend should be compared to the safety data from pivotal clinical trials."

In Study ART 03-001 the Sponsor compared the C_{max} and T_{max} of the two drug formulations following administration of articaine up to the maximum recommended dose (11.9ml) and as per discussion with the clinical pharmacology reviewer, Dr. Nallani, the difference between the two

was not statistically significant which leads to the conclusion that the lower concentration of epinephrine does not alter significantly the systemic exposure to articaine.

5.2 Pharmacodynamics

From the Clinical Pharmacology and Biopharmaceutics Review of NDA 20-971, p.5:

"Following a single dose injection of 1.7 m1of 4% articaine hydrochloride with 1:200,000 epinephrine, the mean time to onset of anesthesia (time to lack of perception at maximum stimulation with a pulp stimulator) was 3.65 ± 0.39 minutes. The mean duration of anesthesia (time from onset of anesthesia to decrease from maximum stimulation by 50%) was 68.20 ± 8.3 minutes."

With studies ART02-001 and ART02-002 the Sponsor evaluated and compared the same pharmacodynamic parameters for the two drug formulations with epinephrine and for articaine without epinephrine.

In Study ART 02-001 the addition of epinephrine did not affect the time to onset or the time of duration of 4% articaine with epinephrine 1:100,000 (A100) and 4% articaine with epinephrine 1:200,000 (A200) compared to 4% articaine without epinephrine (Aw/o), following inferior mandibular block. **All three formulations had similar time to onset and time of duration;** the differences were not statistically significant.

Table 5.2-1 **Time to Onset and Time of Duration of Three Formulations of Articaine After Inferior Mandibular Block** (Table generated with data from the Sponsor's table "Summary of Efficacy Results in Study ART02-001", NDA Vol. 28, p. 37)

	Time to Onset			Time of Duration		
Treatment Groups	n*	Mean ± SD	Range	n*	Mean ± SD	Range
A200	34/62	4.7 ± 2.6	1.0 - 9.0	34/62	51.2 ± 55.9	3.0 - 218.0
A100	30/63	4.2 ± 2.8	0.5 - 9.0	30/63	61.8 ± 59.0	3.5 - 236.0
Aw/o	16/62	4.3 ± 2.5	0.5 - 8.0	16/62	49.7 ± 44.2	3.5 - 161.0

*N=successful anesthesia/patients exposed to the drug

In Study ART 02-002 the addition of epinephrine did not affect the time to onset of any of the three formulations, following maxillary infiltration. All three formulations had similar time to onset. However, the addition of epinephrine prolonged the duration of anesthesia forA100 and A200 compared with Aw/o, following maxillary infiltration. **The anesthesia with A100 and A200 lasted longer than with Aw/o.** The differences were statistically significant.

Table 5.2-2 **Time to Onset and Time of Duration of Three Formulations of Articaine After Maxillary Infiltration** (Table generated with data extracted from NDA Vol. 18, p. 56)

	Time to Onset			Time of Duration		
Treatment Groups	n*	Mean ± SD	Range	n*	Mean ± SD	Range
A200	58/62	3.1 ± 2.3	0.5 – 9.5	58/62	41.6 – 21.1	3.5 – 103.0
A100	60/63	3.0 ± 2.1	0.5 – 9.5	60/63	45.0 – 23.6	5.0 - 99.5
Aw/o	47/62	3.0 ± 2.0	0.5 – 9.5	47/62	13.3 – 6.8	2.0 – 38.0

*n= successes/visits
For further detail please refer to the Clinical Pharmacology Review for this NDA.

5.3 Exposure-Response Relationships

The clinical trials did not indicate a clear exposure-response relationship in terms of efficacy. In all the trials only single dose administrations were explored. In terms of safety higher doses of anesthetic correlated with higher incidence of adverse events (refer to Table 7.4.2.1)

The studies did not include patients over 65 years of age and even in the adult population studied there were few subjects/ patients among the older adults compared to younger adults. The Sponsor did not provide datasets with the patients' ages. This reviewer concluded from the available data that:

- For studies ART 02-001 and ART 02-002 the Sponsor grouped the subjects by age for certain subset analysis in age groups. The distribution of the subjects is displayed in the table below:

Table 5.3-1 **Distribution of Subjects by Age Groups from Studies ART 02-001 and ART02-002** (Created by the reviewer with data from the Sponsor's tables "Percentage of Success by Age Category", Vol.15, p. 93, and Vol. 18, p. 92).

Age Groups	Subjects in ART02-001	Subjects in ART02-002	Total (n=126 subjects)
< 26	29	27	56 (44%)
26-29	14	11	25 (19.8%)
30-39	9	16	25 (19.8%)
>39	11	9	20 (15.8%)

There was a predominance of young adults. The age range in Study ART02-001 was 19-57 years of age and in Study ART 02-002 it was 20-55 years. Therefore there were no patients studied > 57 years old in these two studies.

- For Study ART 02-003 the Sponsor grouped the patients for certain subset analysis as displayed in the table below:

Table 5.3-2 **Distribution of Subjects by Age Groups from Study ART 02-003** (Created by the reviewer with data from the Sponsor's table "Summary of Quantity of Blood Loss by Age Category, Vol. 21, p. 112).

Age Groups	Patients in Art 02-003 (n=42)
<40	7 (16.6%)
40-49	17 (40.4%)
50-59	17 (40.4%)
>59	1 (2.3%)

Since the age range for this study was 22-65 years of age, this reviewer concluded that the only patient in the > 59 age group was 65 years old and that there were no other patients over 59 years old.

- For Study ART 03-001 the Sponsor grouped the subjects by age for certain subset analysis as displayed in the table below:

Table 5.3-3 **Distribution of Subjects by Age Groups from Study ART 03-001** (Created by the reviewer with data from the Sponsor's table "Treatment Summary of time to Maximum Change of Heart Rate from Pre-Dose", Vol. 23, p. 99)

Age Groups	Subjects in ART 03-001 (n=14)
<25	1 (7.1%)
25-29	11 (78.5%)
>30	2 (14.2%)

For this study, in which the maximum recommended dose was used, this reviewer concluded that only young adults were studied. The age range was 24-38 years; therefore, the 2 patients in the > 30 years group were at most 38 years old.

The study population was overall small, but had been agreed upon. In addition, the distribution of the study population according to race was very uneven, with a predominance of White subjects (129/182, 70.8%); therefore, relevant conclusions of the effect and adverse events on different races cannot be drawn.

Pediatric patients did not participate in any of the studies submitted; therefore, no new pediatric information is available for labeling purposes.

The efficacy trials were conducted with single doses of articaine; therefore, recommendations regarding multiple doses and re-dosing cannot be made based on the data submitted.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The proposed package insert, dated September 2005, presents the following indication:

[ ]

6.1.1 Methods

Three of the four studies submitted assessed efficacy. Studies ART 02-001 and ART 02-002 were designed as non-inferiority trials, comparing the rate of successful anesthesia between the two formulations containing epinephrine, and also between these formulations and the anesthetic without epinephrine. In addition, these two studies compared the pharmacodynamic endpoints- time of onset and duration- of the three formulations of articaine.

The third efficacy study ART 02-003 compared the visualization of surgical field between Septocaine — and — by means of a surgeon visualization rating system, by measurement of blood loss during surgical procedures and an expectation of bleeding rating system.

6.1.2 General Discussion of Endpoints

The Sponsor used the following endpoints to assess the efficacy of A200:

- the success rate of A200 for achieving complete anesthesia compared to the approved A100, and the formulation with articaine alone, following submandibular nerve block and mandibular infiltration;
- time of onset and duration of A200 compared to the approved A100 and the formulation with articaine alone;
- the surgeon's rating of the ability to visualize the surgical field using a seven point scale, the Visualization of Surgical Field Scale;

- the surgeon's rating of bleeding using a seven point scale, the Expectation of Blood Loss Scale;
- the comparison of the total amount of blood loss after injection of A200 and A100;
- the rate of failure to achieve adequate surgical hemostasis;
- the comparison of levels of anesthesia for the surgical procedure through patient report of the level of anesthesia and pain control.

The success rate of anesthesia, as well as the time of onset and duration of anesthesia, was assessed by means of an electric pulp tester (EPT). Baseline EPT values had to be between 10 and 50, which indicated adequate pulp vitality. Success was defined as achievement of complete anesthesia (EPT value of 80) by 10 minutes after injection of the study drug. Validation of this test has not been established, but its use has been reported in the literature.

To evaluate hemostasis, the Sponsor used several endpoints. Due to the lack of validated methods to assess blood loss during dental procedures, the Sponsor used two rating systems: the Visualization of Surgical Field Scale and the Expectation of Blood Loss Scale. These rating systems collected information on the surgeons' impression of the clarity of the surgical field and their impression of the amount of blood that was lost during the procedure.

The other method the Sponsor used to assess hemostasis was the measurement of the total blood loss, by estimating the difference between the volume of fluids used during the surgical procedure (irrigation solution and ultrasonic scaler solution) and the volume collected at the end of the procedure by means of an aspirator, plus the difference in weight of the gauze utilized during the procedure. The difference would result in the estimated blood loss.

Another endpoint was the surgeon's ability to perform the surgery without using an alternative anesthetic (2% lidocaine hydrochloride with 1:50,000 epinephrine); failure was defined as the need for an alternative anesthetic to control bleeding and improve visualization.

In all the studies, as a secondary endpoint, the investigator compared levels of anesthesia by eliciting descriptive reports from the patients before and after drug administration. To achieve this, the investigator used responses printed on cards which allowed for quick selection by the subject or patient.

Our Division has consulted the Division of Dermatology and Dental Drug Products about the adequacy of the endpoints chosen (see review dated February 26, 2006).

6.1.3 Study Design

All studies seemed to be adequately blinded and randomized.

Studies ART02-001 and ART02-002 were designed to demonstrate that the new formulation A200 is not inferior to the approved drug A100 and to demonstrate the anesthetic characteristics of A200. The two formulations containing epinephrine were compared to each other, and both were compared to the articaine formulation without epinephrine. The use of articaine without epinephrine instead of a placebo arm was recommended by the Agency, to fulfill the combination drug product requirement. The doses of study drug utilized in these two studies were the minimum efficacious doses, chosen by the Sponsor to minimize exposure to higher levels of drug and to reflect daily clinical practice.

Study ART 02-003 was designed with the intent to demonstrate a difference in hemostasis between the two formulations containing epinephrine. As per previous discussion between in the Sponsor and the Agency, hemostasis could be used to distinguish one formulation from the other for labeling purposes (please refer to Section 2.5 Presubmission Regulatory History). Subjects were exposed to higher doses of study drug, where the doses ranged from 1 to 4 cartridges (1.7 to 6.8ml).

The studies included generally healthy individuals. Subjects or patients with cardiovascular compromise were not included, as recommended by the Agency. Pediatric and geriatric populations were not included.

Study ART 03-001 was designed as a PK study were the Sponsor intended to compare the C_{max} and T_{max} of A100 and A200. Subjects were exposed to the maximum recommended dose of 11.9ml.

6.1.4 Efficacy Findings

The primary objective of **Study ART02-001** was to demonstrate that the new articaine formulation was not inferior to the approved formulation, by comparing the success rate in achieving profound anesthesia by 10 minutes. The overall success rate for the three formulations altogether was 42.8%, which is considerably low. There was a wide variability among the three study sites: University of Pittsburgh, 68.6%, University of Pennsylvania, 39.7%, and The Forsythe Institute, 19.7%.

The percentage of success rate by treatment and by site is displayed in the table below (table created by the reviewer with data provided by the Sponsor on February 10, 2005 and by our statistical reviewer).

Table 6.1.4-1 **Success Rate by Treatment and By Site for Study ART 02-001 (success/patients exposed to drug)**

	Aw/o	A100	A200
Un. Pitts.	5/21 (23.8%)	18/21 (85.7%)	20/21 (95.2%)
Un. Penn.	9/21 (42.9%)	6/21 (28.6%)	10/21 (47.6%)
Forsythe Ins.	2/20 (10.0%)	6/21 (28.6%)	4/20 (20.0%)

A few hypotheses suggested by this reviewer, to explain the variability of the results by site are:

- The difference in the anesthesia technique since the inferior mandibular nerve block is known to incur in more technical difficulties (Moore, PA, Editor, *Manual of Local Anesthesia in Dentistry,* 4th Ed., Eastman-Kodak Co, Rochester, NY, 1996).
- The time point chosen to declare anesthetic success or failure at 10 minutes: some patients may take a longer period of time to respond to the anesthetics and by testing for a longer period of time, the investigator could possibly detect more successful responses.
- In practice, some patients may require more anesthetic and in this trial there was no attempt to give additional doses of anesthetic; this may impact labeling recommendations as to when and how much additional anesthetic can be used for inferior nerve block.

The response to the anesthetic was also variable for the same patient across the treatment arms regardless of the study site. One would expect that a patient who responded to one articaine formulation would respond to the other formulations since the difference is the concentration of epinephrine, but this was not always the case. The table below illustrates the responses of some patients, across the treatment arms (Table created by the reviewer with data extracted from Appendix 10.2.12. Listing of EPT Values and Subject Descriptive Ratings, Vol.17, p. 7, and Appendix 10.1.5. Randomization Schedule, Vol.16, p. 125).

Table 6.1.4-2 **Patients' Success/Failure Responses by Treatment** (sample)
[S=success; F=failure]

	Subject #	Aw/o	A100	A200
Un. Pittsburgh	5	S	F	S
	10	F	F	S
Un. Pennsylvania	25	F	S	F
	35	F	S	F
The Forsythe Ins.	51	F	S	F
	57	F	F	S

The Sponsor was inquired about the rationale for such low response rate, an explanation for the disparity in success rates, and whether subjects and patients received the anesthesia by the same investigator at every visit. The response was dated February 2, 2006.

With a few exceptions, the same investigator injected the subject or patient at every treatment visit. At the University of Pittsburgh, all injections and EPT testing were performed by Dr. ~~~. At the University of Pennsylvania, Dr. ~~~ administered each injection, with the

exception of the third visit for subject 31 which was performed by Dr. EPT testing was performed by Dr. Dr. , or . At The Forsythe Institute, 11 subjects received the injection and EPT testing from a single investigator, either Dr. or Dr. and 9 subjects were treated and EPT tested by a combination of both investigators.

The Sponsor also responded to our questions by submitting literature evidence that the anesthetic success rate is variable. An article by McLean et al, the authors compared the rate of soft tissue anesthesia (reported as response to a needle stick of the oral mucosa) and pulpal anesthesia (by EPT testing up to 16 minutes). Soft tissue anesthesia occurred 100% of the time whereas successful pulpal anesthesia occurred 53-67% of the time. The authors pose that although EPT testing is a more precise assessment of complete profound anesthesia, clinically adequate anesthesia for many restorative procedures may not require complete pulpal anesthesia (EPT 80).

Other articles submitted present different rates of success. Tofoli *et al* had a 100% success rate of EPT using 1ml of articaine 1:100,000 and 1:200,000 epinephrine. Potočnik and Bajrovic report failure rates of 30 to 45% of inferior alveolar nerve block in general. The Sponsor believes that the disparity in anesthetic success rates across the sites was due to differences in operator skill. The Sponsor attributed the high success rate in the University of Pittsburgh, to the fact that the injections were administered by a dentist anesthesiologist.

Despite the results presented, since all patients were treated equally with the three formulations, the analysis the success rate by treatment arms indicate that the difference in success rates between A200 34/62 (54.8%) and A100 30/63 (47.6%) was not statistically significant, p=0.2253.

The patients that were successful in achieving anesthesia were studied to characterize the new formulation A200 in terms of time to onset, time of duration and compared to the approved formulation A100. The anesthetic characteristics for each formulation were very similar and the Sponsor demonstrated that the two drugs have similar pharmacodynamic profile (displayed in Table 6.1.4-2 below).

As a secondary endpoint the Sponsor compared the success rate and anesthetic characteristics of A100 and A200 to Aw/o. The Sponsor successfully demonstrated that A100 and A200 had a higher success rate compared to Aw/o. By analyzing the success cases of the Aw/o treatment arm, the Sponsor demonstrated that the addition of epinephrine did not affect the time of onset. The duration of anesthesia was shorter with Aw/o but the difference was not statistically significant. The efficacy data described is summarized in the table below.

Table 6.1.4-2 **Time of Onset and Time of Duration of Three Formulations of Articaine After Mandibular Block Injection** (Data extracted from NDA Vol. 28, p. 37)

	Time to Onset			Time of Duration		
Treatment Groups	N	Mean ± SD	Range	N	Mean ± SD	Range
A200	34/62	4.7 ± 2.6	1.0 - 9.0	34/62	51.2 ± 55.9	3.0 - 218.0
A100	30/63	4.2 ± 2.8	0.5 - 9.0	30/63	61.8 ± 59.0	3.5 - 236.0
Aw/o	16/62	4.3 ± 2.5	0.5 - 8.0	16/62	49.7 ± 44.2	3.5 - 161.0

As another secondary endpoint the sponsor elicited the subjective rating of anesthesia within the first 10 minutes of the injection of study drug. The percentage of patients with ratings of 3 (moderate but not complete feeling of numbness) or 4 (side of the mouth totally numb) was 77.4% in the Aw/o arm, 87.3% in the A100 arm and 85.5% in the A200 arm.

Study ART 02-002 had a similar design as the study previously described, except that the procedure was the maxillary infiltration and the anesthetic dose used was 1.0ml. The objectives were the same. The primary objective was to demonstrate that the new articaine formulation was not inferior to the approved formulation by comparing the success rate in achieving profound anesthesia by 10 minutes. In this study the overall success rate was higher, 88.2% and the results were consistent across the sites: University of Pittsburgh 88.9%, University of Pennsylvania 90.2% and The Forsythe Institute, 85.7%.

The analyses of success rate by treatment arms demonstrated that the difference in the success rate was not statistically significant between A200 (93.5%) vs. A100 (95.2%), p= 0.6547.

The patients that were successful in achieving anesthesia were studied to characterize the new formulation A200 in terms of time to onset, time of duration and these anesthetic characteristics were compared to the ones of A100. The Sponsor demonstrated that these two drugs have a similar pharmacodynamic profile (displayed in Table 6.1.4-3 below).

As a secondary endpoint the Sponsor compared the success rate and anesthetic characteristics of A100 and A200 to Aw/o. The Sponsor demonstrated that the formulations containing epinephrine had a higher success rate than the formulation without epinephrine: A200 (58/62, 93.5%) vs. Aw/o (47/62, 75.8%), p = 0.0076 and A100 (60/63, 95.2%) vs. Aw/o, p = 0.0013.

The Sponsor also succeeded to demonstrate that the addition of epinephrine did not affect the time to onset of anesthesia, but there was a statistically significant difference in the duration of anesthesia between the formulations containing epinephrine and Aw/o: A200 vs. Aw/o, p<0.0001; A100 vs. Aw/o, p <0.0001. The efficacy data described is summarized in the table below.

Table 6.1.4-3 **Time to Onset and Time of Duration of Three Formulations of Articaine After Maxillary Infiltration** (Table created with data from NDA Vol. 18, p. 56)

	Time to Onset			Time of Duration		
Treatment Groups	N	Mean ± SD	Range	N	Mean ± SD	Range
A200	58/62	3.1 ± 2.3	0.5 – 9.5	58/62	41.6 – 21.1	3.5 – 103.0
A100	60/63	3.0 ± 2.1	0.5 – 9.5	60/63	45.0 – 23.6	5.0 - 99.5
Aw/o	47/62	3.0 ± 2.0	0.5 – 9.5	47/62	13.3 – 6.8	2.0 – 38.0

Study ART 02-003 was designed with the primary objective of demonstrating a difference in hemostasis by using a rating system called the "Visualization of Surgical Field Scale". According to the Sponsor's data, the surgical field was rated as "clear" in 83% of the time with A100 and 59.52% of the time with A200, p= 0.0075. The Sponsor had defined as a "clear surgical field" all the ratings of "5- slightly clear", "6-moderately clear", and "7- very clear".

This reviewer considered this definition very inclusive, particularly because the distinction between "slightly clear" and "slightly unclear" cannot be consistently made; instead, this reviewer analyzed the data using only the extreme ratings, and by grouping the ratings "moderately and very clear" and "very unclear and moderately unclear". The overall success rate in obtaining a clear surgical field would be 57% instead of 71.5% as per the Sponsor's analysis The success rate for A100 would be 61.9% and for A200 47.6%, p= 0.0455, which is statistically significant. On the other hand, the total of visits with truly poor visualization would be for A100 0% and for A200 11.9%, p= 0.0253 which is statistically significant. This analysis indicated that A100 is superior in providing a clearer surgical field and is consistent with the Sponsor's assessment.

A secondary endpoint that was used to evaluate the hemostatic effect of the anesthetics was the measurement of total blood loss. The data presented by the Sponsor indicated that there was less blood loss with A100 (mean 54.9ml) and A200 (mean 70.2ml) and the difference was statistically significant, p= 0.0175. One problem with the data presented was that there were negative collection values for two patients, which suggests that the patients swallowed some of the fluids that were supposed to be aspirated and measured. These are the only two cases that were easily detected because of the negative values recorded. It does not mean, however, that the same problem might have not occurred with other patients, because their recorded aspirates were all positive values. It is possible that some of the fluids could have been swallowed, but there are no means of estimating the volumes lost. The volumes used in each center for the procedures varied considerably and can contribute to inaccuracy of the method for measuring the blood loss.

The data was re-analyzed by the statistical reviewer who eliminated the two cases with negative blood loss and the difference between the two arms was statistically significant: A100 (mean 58.04ml) vs. A200 (mean 70.22ml), p= 0.0174. Further analyses of the blood loss data by the statistical reviewer revealed discrepancies among the study sites but there was a trend in favor of less blood loss with A100 compared with A200 (Refer to Table 10.1.3.14-1).

Despite the concerns about the accuracy of the method used for this secondary endpoint, it is fair to say that there is a trend of less blood loss with the formulation A100 but the data cannot support any claims in regards to blood loss.

Another secondary endpoint was the surgeon's expectation of blood loss by using a rating scale called The Expectation of Blood Loss Scale. At the end of the procedure the surgeon would rate the bleeding in comparison to his or her past experience with periodontal surgery. The Sponsor claimed that the expectation of blood loss was ranked equal or less in 85.71% of the time with A100 and 71.43% of the time with A200. Since there are no known validated assessment tools for this type of assessment, this reviewer chose to analyze only the treatment visits that ranked as "moderately better and much better than expected" not including the treatments that were rated as 'slightly better" because of the lack of clear distinction between "slightly better" and "slightly worse". The analyses revealed that the hemostasis was considered better in 30.9% of the treatments for A100 and 26.1% for A200 and the difference is not statistically significant, $p=$ 0.593.

The subjective rating of anesthesia was elicited in all the studies but only in study ART 02-001 was analyzed by the Sponsor. The analysis of this rating for all the studies was requested from the Sponsor. The Sponsor submitted the data on March 9, 2006. This reviewer analyzed the subjective rating of anesthesia for all the studies. In studies ART 02-001 and ART 02-002, the rating of 4-"Completely numb" is what correlates best with the endpoint of EPT $\geq$ 80.

In Study ART 02-001 one would expect that at 10 minutes post-dose the same percentage of patients who had an EPT $\geq$ 80 would also report as being "completely numb". However, not all subjects that had "profound anesthesia" by EPT reported being "completely numb" with the epinephrine containing formulations and some subjects in the articaine alone did feel complete numbness despite the fact that they did not reach an EPT $\geq$80. The incidence of the rating "completely numb" was low, similar to the success rate by EPT. The data for comparison is listed in the table below (table created by the reviewer).

Table 6.1.4-4 **The Success Rate by EPT and the Subjective Rating of Complete Anesthesia at 10 minutes Post-Dose by Treatment Arm for Study ART 02-001**

	Aw/o	A100	A200
EPT $\geq$ 80	16/62 (25.8%)	30/63 (47.6%)	34/62 (54.8%)
"Completely numb"	20/62 (32.3%)	25/63 (39.7%)	25/62 (40.3%)

The descriptive rating of 4 occurred at a higher incidence in Study ART 02-002. The rationale for the discrepancy in the results between the two studies was described previously in this section. Fewer subjects rated their level of anesthesia as being "completely numb", compared to the number of subjects that had EPT values $\geq$ 80. The data for comparison is listed in the table below (table created by the reviewer).

Table 6.1.4-5 **The Success Rate by EPT and the Subjective Rating of Complete Anesthesia at 10 minutes Post-Dose by Treatment Arm for Study ART 02-002**

	Aw/o	A100	A200
EPT ≥ 80	47/62 (75.8%)	60/63 (95.2%)	58/62 (93.5%)
"Completely numb"	38/62 (61.3 %)	50/63 (79.4 %)	47/62 (75.8 %)

In Study ART 02-003 the subjective ratings of anesthesia did not lead to any conclusions because many of the patients rated their level of anesthesia as 2 and 3 and it was not clear whether in this situation they received more anesthetic to proceed with the surgery (see Table10.1.3.13.2)

On the other hand, in Study ART03-001 where the patients received up to 11.9ml of anesthetic one would expect nearly all patients to be completely numb and the data demonstrated that several patients rated their level of anesthesia as moderate despite the large volume of anesthetic administered (see Table 10.1.4.14.2). This reviewer could not make any conclusions in this study whether a subject rating of 3 would be sufficient to tolerate a painful procedure.

6.1.5 Clinical Microbiology

This section is not applicable as the drug product is not an antimicrobial.

6.1.6 Efficacy Conclusions

The Sponsor developed a program to demonstrate the non-inferiority of articaine 4% with epinephrine 1:200,000 compared with the approved formulation containing epinephrine 1:100,000. As the statistical reviewer stated in his review, despite the variable and low overall success rates across the sites in ART 02-001, this concern was compensated by the fact that each subject served as its own control in the crossover trial. Therefore both studies ART 02-001 and ART02-002 successfully demonstrated that the new formulation is not inferior to the approved product in terms of success rate and the anesthetic characteristics- time to onset and duration.

The Sponsor also conducted the studies with the intention of finding a characteristic that would distinguish one formulation from the other for the purpose of more accurately labeling the two products. The Sponsor pursued to demonstrate a difference in hemostasis. This was achieved with the analyses of the Visualization of Surgical Field Scale from ART 02-003, and by using more stringent analyses of the results, this reviewer concluded that the formulation with 1:100,000 epinephrine does allow better visualization of the surgical field.

This reviewer concluded that both formulations are equally effective, and the use of the formulation A100 can be recommended when better visualization is required.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

Data from the clinical trials, as well as a search from the Adverse Events Reporting System (AERS) and MEDWATCH were reviewed in support of the safety of 4% articaine with epinephrine 1:200,000.

7.1.1 Deaths

No deaths occurred in any of the human subjects or patients during the studies with articaine in this NDA.

7.1.2 Other Serious Adverse Events

No serious adverse events were reported for any of the human subjects or patients during the studies with articaine in this NDA. All reported adverse events were considered mild or moderate in intensity.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

Of the 182 subjects and patients who participated in the clinical trials for this drug product, one withdrew consent from Study ART02-001, one was withdrawn from Study ART02-002 due to a protocol violation, all completed study ART02-003, and one withdrew consent from ART 03-

001. According to the Sponsor, none of the patients withdrew due to an adverse event. The Case Report Forms for the patients who withdrew or were withdrawn from the studies were requested from the Sponsor, and were sent in correspondence dated February 10, 2006 (refer to section 7.1.3.2).

7.1.3.2 Adverse events associated with dropouts

According to the Sponsor, none of the subjects who withdrew from the clinical trials did so due to an adverse event. The reason for withdrawal was not provided in the submission. Copies of the CRF for these patients were requested and sent by the Sponsor in the Response to Requests for Additional Information dated February 10, 2006. Subject 45 of Study ART 02-001 and Subject 3 of Study ART 03-001 both withdrew consent after their first visits. The CRFs of these subjects do not provide a reason for withdrawal. The first subject had discomfort of moderate intensity and the second subject had a sty of mild intensity. One subject in Study ART02-002 was withdrawn after the first visit due to a protocol violation: the investigator stopped recording the EPT values when the patient achieved an EPT value < 80, when the patient should have had three consecutive EPT values < 80 as evidence of loss of analgesia.

7.1.3.3 Other significant adverse events

One patient in Study ART02-001 presented a vasovagal syncope that started two minutes after initiation of the injection and resolved within 10 minutes with reverse Trendelenburg positioning and oxygen by canula. The patient continued the treatment session.

There were 3 reports of paresthesias (numbness and tingling): 2 of them were treated with A100 and 1with A200. All of them resolved within 24 hours without treatment.

7.1.4 Other Search Strategies

Adverse events were evaluated in terms of demographic frequency. No special search strategies were utilized in the course of this review although an integrated safety database had to be created by the reviewer from the individual study data tables provided.

7.1.5 Common Adverse Events

There were a total of 182 patients/subjects enrolled in the clinical studies.

There were 182 treatments with 4% articaine with 1:100,000 epinephrine, 179 with 4% articaine with 1:200,000 and 124 treatments with 4% articaine without epinephrine. The administration of the drug was via infiltration or nerve block.

According to the Sponsor there were:

- 38 (21.2%) adverse events reported among the 179 exposures to 4% articaine with 1:200,000 epinephrine
- 49 (26.9%) adverse events reported among the 182 exposures to 4% articaine with 1:100,000 epinephrine
- 20 (16.1%) adverse events reported among 124 exposures to 4% articaine without epinephrine

7.1.5.1 Eliciting adverse events data in the development program

The adverse events were to be assessed immediately following the treatment visit and at a 24-hour telephone interview.

Immediately following the treatment visit the investigator would respond to an assessment which included yes/no questions to the following: "Did any of the following reactions occur following the anesthetic administration today: Unexpected pain upon injection? Positive aspiration during injection? Discomfort at the injection site? Swelling at the site of injection (hematoma)? Rash or other abnormal skin reaction? Syncope? Other?" If the answer was yes to any of the questions the adverse events were to be described on the Adverse Event Form in the CRF. This was the investigator assessment for all the studies.

For all the studies a 24-hour post-treatment telephone call was to be conducted. The investigator or site personnel would elicit adverse events by asking the subject or patient a yes/no question; "Have you noticed any changes in your health since yesterday's testing?" A positive response would be followed by a series of questions from a checklist to define the location and a description of the adverse event. The subjects were to be asked specifically about local reactions with the yes/no question: "Have you noticed any of the following reactions in your mouth or face since your procedure yesterday: Swelling? Headache? Infection? Persistent pain? Gingivitis? Numbness or tingling? Other?" This was the 24-hour phone assessment for Studies ART 02-001 ART 02-002 and ART 03-001. For Study ART02-003 the assessment did not include the questions: swelling, persistent pain, gingivitis. Any positive answer to the assessment described was to be recorded on the CRF. An immediate return visit to the office was to be arranged if any adverse event was considered severe or requiring treatment.

For the patients in Study ART 02-003, another adverse event assessment was to be made at the 7-day post-operative visit. Following suture removal, post-operative recovery and wound healing were assessed. The investigator was to answer (yes/no) whether recovery and wound healing were acceptable. Specific oral complications or adverse events were elicited the same way as in the 24-hour phone call questionnaire. At this follow-up the list of questions was more comprehensive and included: swelling, headache, infection, persistent pain, gingivitis, numbness or tingling, persistent bleeding, poor wound healing, other. Any positive response at this post-operative assessment would require a description of the adverse event on the Adverse Event Form in the CRF.

In neither of the studies the subjects/patients were asked questions that would elicit reports of other adverse events that may occur with anesthetics such as sleepiness, drowsiness, grogginess, lethargy, lightheadedness, seizures; tingling or numbness in other locations of the body besides the oral area were not specifically inquired.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Descriptive terms of the adverse events were to be recorded by the investigators and coded to the COSTART dictionary. Using the COSTART terms, adverse events were to be, tabulated by body system for each treatment group as well as by maximum intensity and relationship to study drug for Studies ART02-001 and ART02-002. Study ART02-003 was amended to remove the reference to COSTART terminology for adverse events. Adverse events for ART 03-001 were to be tabulated by body system for each treatment group. Adverse events for all the studies were listed verbatim from the CRF. The Sponsor had not presented the list of adverse events with the COSTART terms which had been proposed in ART 02-001 and ART 02-002, and was not available at the time of this review. The listing of all adverse events with the COSTART terms has been requested, but is not available at the time of this review. This reviewer categorized the events in order to conduct the review.

The Sponsor sent later in the review (response to Request for Additional Information dated February 10, 2006) a table listing all the adverse events using COSTART terminology. The review of the listing did not alter this reviewer's conclusions in regards to the adverse events reported.

7.1.5.3 Incidence of common adverse events

The Sponsor chose to group the adverse events from Studies ART 02-001 and ART02-001 because of their similar design and similar treatment doses. Studies ART 02-003 and ART 03-

001 were analyzed individually. The Sponsor did not provide an integrated safety review of the four studies altogether.

This reviewer's assessment for **ART02-001** revealed that there were 48 reported adverse events that occurred for 25 of the 63 subjects enrolled, over 187 visits. The Sponsor reported 44 events that occurred for 25 enrolled subjects. The discrepancy in the numbers is because this reviewer chose to count the following adverse events independently, whereas the Sponsor had them grouped:
Subject 45: soreness of neck and shoulder and sensitive teeth
Subject 45: soreness at injection site and earache
Subject 49: headache and soreness at injection site
Subject 50: swelling and soreness at injection site

All subjects in this study were to receive 1.7ml of study drug for **inferior mandibular block.** For the analyses of the incidence of adverse events this reviewer grouped some of the reports as displayed on the Table 7.1.5.3-1. The distribution of the adverse events was as follows:

Table 7.1.5.3-1 **Adverse Events Reported for Study ART 02-001** (n= patients exposed to drug)

Adverse Event	A100 (n=63)	A200 (n=62)	Aw/o (n=62)
Pain	8 (12.6%)	5 (8.0%)	5 (8.0%)
Soreness at injection site	5 (7.9%)	4 (6.4%)	4 (6.4%)
Unexpected pain upon injection	0 (0%)	0 (0%)	1 (1.6%)
Persistent pain	1 (1.5%)	1 (1.6%)	0 (0%)
Sensitive teeth	1 (1.5%)	0 (0%)	0 (0%)
Soreness of neck and shoulder	1 (1.5%)	0 (0%)	0 (0%)
Positive blood aspiration into syringe	5 (7.9%)	1 (1.6%)	3 (4.8%)
Headache*	2 (3.1%)	4 (6.4%)	2 (3.2)
Gastric symptoms	0 (3.1%)	1 (1.6%)	2 (3.2%)
Nausea	0 (0%)	1 (1.6%)	0 (0%)
Heartburn	0 (0%)	0 (0%)	2 (3.2%)
Elevated blood pressure	0 (0%)	1 (1.6%)	1 (1.6%)
Trismus	1 (1.5%)	0 (0%)	1 (1.6%)
Ear symptoms	1 (1.5%)	1 (1.6%)	0 (0%)
Earache	1 (1.5%)	0 (0%)	0 (0%)
Otitis media	0 (0%)	1 (1.6%)	0 (0%)
Numbness and tingling	1 (1.5%)	0 (0%)	0 (0%)
Swelling	0 (0%)	0 (0%)	1 (1.6%)
Urticaria	0 (0%)	0 (0%)	1 (1.6%)
Vasovagal syncope	0 (0%)	0 (0%)	1 (1.6%)
Total	18 (28.5%)	13 (20.96%)	17 (27.4%)

* One report was: "Subject had an electronic shock to the head, subject hit head on chandelier. Subject went to the ER and received Tylenol."

All adverse events were of mild or moderate intensity. None of the adverse events were serious.

The rate of adverse events by treatment group is as follows: A100 18/63 (28.5%), A200 13/62 (20.96%), Aw/o 17/62 (27.4%). The difference between A100 and A200 was marginally statistically significant (p= 0.0491).

The most common side effects reported overall were: pain 18/187, positive blood aspiration into syringe 9/187, headache 8/187, gastric symptoms 3/187. Other reports of interest are trismus 2/187 (one event in the A100 group and other in the Aw/o group), numbness and tingling 1/187 (A100 group), vasovagal syncope 1/187 (Aw/o group).

This reviewer's assessment for **ART02-002** concluded that there were 19 adverse events that occurred for 14 of the 63 subjects enrolled, over 187 visits. The Sponsor reported 18 adverse events for 14 of the 63 subjects enrolled. This discrepancy is due to the fact that this reviewer chose to count independently the following adverse events:
Subject 44: headache and sinus pain.

All subjects in this study were to receive 1.0 ml of study drug for **mandibular infiltration**. For the analyses of the incidence of adverse events, this reviewer grouped some of the reports as displayed on Table 7.1.5.3-2 (below). The distribution of the adverse events was as follows:

Table 7.1.5.3-2 **Adverse Events Reported for Study ART 02-002** (n= patients exposed to drug)

Adverse Event	A100 (n=63)	A200 (n=62)	Aw/o (n=62)
Headache	2 (3.1%)	3 (4.8%)	1 (1.6%)
Pain	1 (1.5%)	1 (1.6%)	2 (3.2%)
Soreness at injection site	1 (1.5%)	0 (0%)	1 (1.6%)
Unexpected pain upon injection	0 (0%)	1 (1.6%)	1 (1.6%)
Sinus symptoms	1 (1.5%)	1 (1.6%)	0 (0%)
Sinus pain	1 (1.5%)	0 (0%)	0 (0%)
Sinus congestion	0 (0%)	1(1.6%)	0 (0%)
Positive aspiration of blood into syringe	0 (0%)	1 (1.6%)	0 (0%)
Elevated blood pressure	1 (1.5%)	0 (0%)	0 (0%)
Numbness and tingling	0 (0%)	1 (1.6%)	0 (0%)
Oral lesions	0 (0%)	0 (0%)	1 (1.6%)
Itchy throat, persistent cough	1 (1.5%)	0 (0%)	0 (0%)
Nausea	0 (0%)	1 (1.6%)	0 (0%)
Anemia	1 (1.5%)	0 (0%)	0 (0%)
Total	7 (11.1%)	8 (12.9%)	4 (6.4%)

All the adverse events were of mild to moderate intensity. None of the adverse events were serious.

One of the cases of pain was reported as soreness at injection site but information sent by the Sponsor later in the review reports that the patient experienced a "shooting pain towards ear on injection". This reviewer chose to list this event as "unexpected pain upon injection".

The rate of adverse events by treatment group was 7/63 (11.1%) for A100, 8/62 (12.9%) for A200 and 4/62 (6.4%) for Aw/o. The rate of adverse events for A100 and A200 was the same (p=0.5375).

The most common side effects reported overall were: headache 6/187, pain 4/187, sinus symptoms 2/187. Other report of special interest was numbness and tingling 1/187 which occurred in the A200 group.

This reviewer's assessment for **ART02-003** concluded that there were 28 adverse events that occurred for 16 of the 42 patients enrolled, over 84 visits. The Sponsor reported 27 adverse event reports for 16 of the 42 patients enrolled. This discrepancy is due to the fact that this reviewer chose to count two adverse event reports as independent:
Subject 11: Post-op swelling and pain.

The subjects in this study received various amounts of anesthetic, up to 6.8ml (4 cartridges) of either A100 or A200 per visit, for periodontal surgery. The formulation without epinephrine was not used in this study. The distribution of the adverse events was as follows:

Table 7.1.5.3-3 **Adverse Events Reported for Study ART 02-003** (n= patients exposed to drug)

Adverse Event	A100 (n=42)	A200 (n=42)	Total
Pain	4 (9.5%)	6 (14.2%)	9
Pain	0 (0%)	3 (7.1%)	3
Soreness	0 (0%)	1 (2.3%)	1
Persistent pain	2 (4.7%)	0 (0%)	2
Intermitent pain	0 (0%)	1 (2.3%)	1
Mild discomfort	1 (2.3%)	1 (2.3%)	2
Cold sensitivity to tooth	1 (2.3%)	0 (0%)	1
Swelling	5 (11.9%)	3 (7.1%)	8
Swelling	2 (4.7%)	2 (4.7%)	4
Swelling upper lip	1 (2.3%)	0 (0%)	1
Slight swelling	1 (2.3%)	0 (0%)	1
Facial swelling R side	1 (2.3%)	1(2.3%)	2
Headache	1 (2.3%)	0 (0%)	1
Numbness and tingling	1 (2.3%)	0 (0%)	1
Burning sensation above inj. site	0 (0%)	1 (2.3%)	1
Ear symptoms	1 (2.3%)	0 (0%)	1
Earache	1 (2.3%)	0 (0%)	1
Runny nose, cold symptoms	1 (2.3%)	0 (0%)	1
Loose tooth	1 (2.3%)	0 (0%)	1

Adverse Event	A100 (n=42)	A200 (n=42)	Total
MO restored with dycal and amalgam	0 (0%)	1 (2.3%)	1
Emesis	0 (0%)	1 (2.3%)	1
Angular cheilitis	0 (0%)	1 (2.3%)	1
Fractured toe	1 (2.3%)	0 (0%)	1
Total	15 (35.7%)	13 (30.9%)	27

All the adverse events were of mild to moderate intensity. None of the adverse events were serious.

The distribution of the adverse events by treatment group was as follows: A100 15/42 (35.7%) and A200 13/42 (30.9%). The difference was not statistically significant (p=0.3545).

For the analyses of the incidence of adverse events this reviewer grouped some of the reports as displayed on the Table 3. The most common side effects reported overall were: pain 9/84, swelling 8/84, and headache 1/84. Other report of interest was numbness and tingling 1/84 which occurred in the A100 group. The case of "burning sensation above the injection site" was in fact underneath the right eye, and as commented by the investigator, during infiltration the anesthetic needle could have contacted the infraorbital nerve

This reviewer's assessment for **ART03-001** concluded that there were 18 adverse events that occurred for 12 of the14 subjects enrolled, over 27 visits. The Sponsor reported the same number of adverse events. All subjects in this study received 11.9ml (7 cartridges) of either A100 or A200 per treatment session for PK sampling. The formulation without epinephrine was not used in this study.

For the analyses of the incidence of adverse events this reviewer grouped some of the reports as displayed on Table 7.1.5.3-4. The distribution of the adverse events was as follows:

Table 7.1.5.3-4 **Adverse Events Reported for Study ART03-001** (n=patients exposed to drug)

Adverse Event	A100 (n=14)	A200 (n=13)
Headache	1 (7.1%)	2 (15.3%)
Sleepiness	1 (7.1%)	2 (15.3%)
Trismus	2 (14.2%)	1 (7.6%)
Palpitation	2 (14.2%)	0 (0%)
Positive blood aspiration into syringe	1 (7.1%)	1 (7.6%)
Pain Soreness	1 (7.1%) 1 (7.1%)	0 (0%) 0 (0%)
Stiff neck	1 (7.1%)	0 (0%)
Cough	1 (7.1%)	0 (0%)
Sore throat	1 (7.1%)	0 (0%)
Sty	1 (7.1%)	0 (0%)
Total	12 (85.7%)	6 (46.1%)

The distribution of the adverse events by treatment group was as follows: A100 12/14, 85.7% and A200 6/13, 46.1%. The difference in the rate of adverse events was significantly higher in the A100 treatment group compared with the A200 group (p= 0.00001).

The most common side effects reported overall were: headache 3/27, sleepiness 3/27, trismus 3/27, palpitation 2/27, positive blood aspiration into syringe 2/27.

The two adverse events *sleepiness* (1 in the A100 group and 2 in the A200 group) and *palpitation* (2 in the A100 group) were only detected in this study where the maximum dose was used.

7.1.5.4 Common adverse event tables

The adverse events that occurred at a frequency >1% in all studies combined is displayed below (does not include adverse events reported in the Aw/o treatment arm):

Table 7.1.5.4-1 **Adverse Events that Occurred >1% by Treatment** (N=patients exposed to drug)

Number of patients exposed to drug	A100 (N= 182)	A200 (N=179)
Number of patients that reported any Adverse Event	35	33
Pain	14 (7.6%)	11 (6.1%)
Headache	6 (3.2%)	9 (5.0%)
Positive blood aspiration into syringe	6 (3.2%)	3 (1.6%)
Swelling	5 (2.7%)	3 (1.6%)
Trismus	3 (1.6%)	1 (0.5%)
Nausea and emesis	0 (0%)	3 (1.6%)
Sleepiness	1 (0.5%)	2 (1.1%)
Numbness and tingling	2 (1.0%)	1 (0.5%)
Palpitation	2 (1.0%)	0 (0%)
Ear symptoms (earache, otitis media)	2 (1.0%)	1 (0.5%)
Cough, persistent cough	2 (1.0%)	0 (0%)
Total	43 (23.6%)	34 (18.9%)

There were more adverse events that occurred at a frequency >1% in the A100 treatment group (23.6%) than in the A200 group (18.9%) and the difference was statistically significant (p=0.0316).

7.1.5.5 Identifying common and drug-related adverse events

The lack of a drug-free placebo makes it difficult to confidently attribute adverse events to the study drug. However, the following adverse events occurred with consistency across the studies with the study drug: pain, headache, and swelling. Because of the known adverse effects associated with local anesthetics and epinephrine (refer to section 2.4 Important Issues With Pharmacologically Related Products), it is conceivable that the adverse events sleepiness and palpitations are related to the higher doses that the individuals were exposed.

7.1.5.6 Additional analyses and explorations

The adverse events such sleepiness and palpitation were only detected in Study ART 03-001 where the patients were exposed to the maximum recommended dose of the study drug (11.9ml). As pointed in the reviewer's assessment in Section 7.1.5.1 Eliciting adverse events in the development program, specific questions addressing sleepiness, drowsiness, grogginess were not elicited. From the dataset submitted by the Sponsor, it is not possible to assess the time that elapsed between treatment and the onset of the adverse event symptoms, however, all were resolved by the end of the studies.

Due to the small number of subjects and patients in the studies and the uneven racial distribution, this reviewer cannot make any meaningful conclusions in regards to the role of these demographics in the adverse event profile of the study drug.

Explorations of drug-disease and drug-drug interaction could not be assessed since the enrollees were mostly healthy and the studies excluded subjects/patients that were taking several drugs such as nonselective beta-blockers, monoamine inhibitors, tricyclic anti-depressants, phenothiazine, butyrophenones, vasopressor drugs , ergot-type oxytocic drugs, aspirin, acetaminophen, non-steroidal anti-inflammatory drugs, opioids or any other analgesics and pre-sedative medications.

An exploration between adverse events and concomitant medications was made by the reviewer and no correlation between the two was found.

7.1.6 Less Common Adverse Events

The less common adverse events (<1%) is displayed below (does not include adverse events reported in the Aw/o treatment arm):

Table 7.1.6-1 **Less Common Adverse Events** (N= patients exposed to drug)

Adverse Event	A100 (N=182)	A200 (N=179)
Burning sensation above injection site	0 (0%)	1 (0.05%)
Runny nose , cold symptoms	1 (0.05%)	0 (0%)
Loose tooth	1 (0.05%)	0 (0%)
MO restored with dycal and amalgam	0 (0%)	1 (0.05%)
Angular cheilitis	0 (0%)	1 (0.05%)
Fractured toe	1 (0.05%)	0 (0%)
Elevated blood pressure	1 (0.05%)	1 (0.05%)
Itchy throat, persistent cough	1 (0.05%)	0 (0%)
Sinus symptoms (pain, congestion)	1 (0.05%)	1 (0.05%)
Anemia	1 (0.05%)	0 (0%)
Stiff neck	1 (0.05%)	0 (0%)
Sore throat	1 (0.05%)	0 (0%)
Sty	1 (0.05%)	0 (0%)
Total	10 (5.4%)	5 (2.7%)

Because of the small population size one cannot make any meaningful conclusion about the correlation of the less common adverse events with the drug use. Nevertheless, there were more adverse events reported in the A100 treatment arm than in the A200 treatment arm.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

Laboratory testing was limited to urine pregnancy testing for all female of childbearing age at screening, and at the days of each treatment visit prior to drug administration in all studies. In addition, for study ART 03-001, baseline hematology labs were performed which included hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, platelet count and INR (International Normalized Ratio) for screening purposes. Subjects were only included in the study if the laboratory values were within the normal range as per the reference laboratory.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

Not applicable to this NDA.

7.1.7.3 Standard analyses and explorations of laboratory data

Not applicable to this NDA.

7.1.7.4 Additional analyses and explorations

Not applicable to this NDA.

7.1.7.5 Special assessments

Not applicable to this NDA.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Vital signs assessment included baseline measurements of supine blood pressure, pulse rate and respiratory rate at screening and prior to drug administration for ART02-001, ART02-002, ART02-003, and ART03-001. These vital signs were repeated at 5 minutes post-dose for ART02-001 and at 10 minutes post-dose for ART02-002 and ART02-003. The same set of vital signs was repeated at the end of the study session in all studies.

Vital signs assessment for ART03-001 included cardiovascular responses by using an acoustic tonometer. The measurements included heart rate, systolic blood pressure, diastolic blood pressure, mean blood pressure, stroke volume, estimated cardiac output, large artery elasticity index, small artery elasticity index and systemic vascular resistance and all maximum changes from baseline were to be determined for each subject, in each session. These measurements were obtained prior to administration of study drug and every 10 minutes following administration of the study drug, up to 120 minutes.

Body weight was obtained at screening for all subjects and patients.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

The time point that was used for ART02-001 is probably adequate for detecting a systemic effect of epinephrine since the route of administration was submucosal, and a few minutes would be necessary for some systemic absorption to occur. For the other studies an additional set of vital signs at 5 minutes post-dose might have been informative. Continuous monitoring of the heart rate for the first 5 to 10 minutes would have been a better method to detect a rapid and transient increase in heart rate, especially if intravenous injection of the study drug had occurred.

7.1.8.3 Standard analyses and explorations of vital signs data

In **Study ART 02-001**, the Sponsor proposed to demonstrate the change in blood pressure and heart rate, following administration of the three formulations. There were small increases in pulse rate and decreases in diastolic blood pressure that were statistically significant but not clinically relevant:

Pulse rate:

- The difference in mean pulse rate and standard deviation from pre-treatment to 5 minutes post-dose between A100 (77.3 ± 11.3 beats /min) and Aw/o (73.3 ± 12.0 beats/min) was statistically significant (p=0.0320).
- The difference in mean pulse rate and standard deviation from pre-treatment to 5 minutes post-dose between A200 (77.5 ± 11.6 beats /min) and Aw/o (73.3 ± 12.0 beats/min) was statistically significant (p= 0.0293).
- There was a statistically significant increase in the **mean changes** in pulse rate from pre-treatment to 5 minutes post-dose for both formulations with epinephrine: A100 increased 3.3 beats/min, p= 0.0051 and A200 increased 2.5 beats/min, p= 0.0064).
- There was a statistically significant difference of the **mean change** in pulse rate from pre-treatment to 5 minutes post-dose, between A100 and Aw/o: A100 increased 3.3 beats/min and Aw/o decreased 1.9 beats/min (p= 0.0005).
- There was a statistically significant difference of the **mean change** in pulse rate from pre-treatment to 5 minutes post-dose, between A200 and Aw/o: A200 increased 2.5 beats /min and Aw/o decreased 1.9 beats/min (p= 0.0016).
- Only A200 showed a decrease in pulse rate from pre-treatment to post-treatment: A200 decreased 2.4 beats/min, which was marginally statistically significant.

Blood pressure:

- A100 and A200, both showed small (2-4 mmHg) but statistically significant decreases in diastolic blood pressure from pre-treatment to 5-minutes post-dose (p= 0.0002 and 0.0062 respectively). The change however, was the same when comparing both of them.
- All three treatments, showed a statistically significant decrease in diastolic blood pressure from pre-to post-treatment.
- There was a statistically significant difference in diastolic blood pressure from pre-treatment to 5 minutes post-dose between A100 and Aw/o (p= 0.0302 based on the Wilcoxon Signed Rank Sum Test).
- Only A100 showed a statistically significant decrease in systolic blood pressure from pre-treatment to 5 minutes post-treatment (2.6 mmHg, p = 0.0153).
- There were no statistically significant differences with the pairwise treatment comparisons of A100, A200 and Aw/o for diastolic blood pressure from pre to post treatment indicating it changed for all three treatments by a similar amount.

Respiratory rate:

- There were no significant changes in respiratory rate for any of the treatments from pre to post-treatment.

Despite the statistically significant changes in the vital signs described above, none of them are clinically relevant.

In **Study ART 02-002**, the changes from baseline to 10 minutes post-dose and post-treatment were minor and of no clinical significance. Some changes in vital signs were statistically significant:

Pulse rate:

- The difference in mean pulse rate and standard deviation from pre-treatment to 5 minutes post-dose between A100 (73.8 ± 11.8 beats/min) and Aw/o (69.8 ± 11.9 beats/min) was statistically significant (p=0.036).
- The difference in mean pulse rate and standard deviation from pre-treatment to 5 minutes post-dose between A200 (73.0 ± 11.5 beats /min) and Aw/o (69.8 ± 11.9 beats/min) was statistically significant (p=0.0175).
- There was a statistically significant difference in the **mean change** of pulse rate and standard deviation between A100 (-0.1 ± 7.5 beats/ min) and Aw/o (-3.6 ± 8.5 beats/min), p= 0.0016.
- The **mean change** in pulse rate for all the drugs was -3.0 beats per minute for Aw/o, -3.8 beats per minutes for A100, and -3.6 beats /minute for A200.

Blood pressure:

- The difference for the mean diastolic blood pressure and standard deviation at 10 minutes post-dose between Aw/o (70.3 ± 7.8mmHg) vs. A200 (67.5 ± 8.4mmHg) was statistically significant, p= 0.0177.
- The difference for the mean diastolic blood pressure and standard deviation at 10 minutes post-dose between Aw/o (70.3 ± 7.8mmHg) vs. A100 (67.4 ± 8.5mmHg), p= 0.0010.

Respiratory rate:

- There were no important changes in the respiratory rates from pre-treatment to 10 minutes post-dose and to post-treatment.

Despite the fact that these changes are statistically significant, none of these changes are clinically relevant.

The following tables are the Sponsor's summaries of the vital signs changes in studies ART 02-001 and ART 02-002 (NDA Vol.28, p. 160):

Table 7.1.8.3-1 **Summary of Means and Mean Changes from Pre-Treatment to Post-Treatment in Vital Signs for ART-02-001 and ART02-002 – Combined Pulse Rate**

Assessment	4% Articaine HCl without Epinephrine	4% Articaine HCl with 1:200,000 Epinephrine	4% Articaine HCl with 1:100,000 Epinephrine	All Articaine Combined
Pulse Rate (beats/minute)				
Pretreatment				
N	124	124	126	374
Mean ± SD	74.3 ± 11.5	74.7 ± 11.3	73.8 ± 11.0	74.3 ± 11.2
Range	44.0-101.0	50.0-107.0	49.0-105.0	44.0-107.0
P-value[a]:				
A200 vs. 100		0.4488	-	
A200 vs. A w/o		0.7990	-	
A100 vs. A w/o		-	0.4491	
Post-treatment				
N	123	124	126	373
Mean ± SD	72.5 ± 11.2	71.7 ± 12.1	71.2 ± 11.4	71.8 ± 11.5
Range	48.0-103.0	46.0-109.0	48.0-108.0	46.0-109.0
P-value [a]:				
A200 vs. 100		0.9342	-	
A200 vs. A w/o		0.5739	-	
A100 vs. A w/o		-	0.3389	
Change from Pre- to Post-treatment				
N	123	124	126	373
Mean ± SD	-1.8 ± 8.7	-3.0 ± 8.6	-2.6 ± 10.5	-2.5 ± 9.3
Range	-21.0 – 25.0	-27.0 – 18.0	-38.0 – 23.0	-38.0 – 25.0
P-value [a]:				
A200 vs. 100		0.7956	-	
A200 vs. A w/o		0.2803	-	
A100 vs. A w/o		-	0.8175	

[a] P-value derived from Wilcoxon signed rank test.
Extracted from Tables 9.1.2 (pretreatment), 9.1.4 (post-treatment), 9.1.6 (change pre-post)

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Table 7.1.8.3-3 **Summary of Means and Mean Changes from Pre-Treatment to Post-Treatment in Vital Signs for ART-02-001 and ART02-002 – Combined Systolic Blood Pressure**

Assessment	4% Articaine HCl without Epinephrine	4% Articaine HCl with 1:200,000 Epinephrine	4% Articaine HCl with 1:100,000 Epinephrine	All Articaine Combined
Systolic Blood Pressure (mmHg)				
Pretreatment				
N	124	124	126	374
Mean ± SD	122.7 ± 11.3	123.0 ± 11.3	123.4 ± 11.5	123.1 ± 11.3
Range	97.0-150.0	76.0-152.0	98.0-153.0	76.0-153.0
P-value [a]:				
A200 vs. 100		0.9472	-	
A200 vs. A w/o		0.6433	-	
A100 vs. A w/o		-	0.2755	
Post-treatment				
N	123	124	126	373
Mean ± SD	121.3 ± 11.0	120.8 ± 11.1	120.8 ± 11.0	121.0 ± 11.1
Range	93.0-148.0	98.0-147.0	95.0-147.0	93.0-148.0
P-value [a]:				
A200 vs. 100		0.9863	-	
A200 vs. A w/o		0.4105	-	
A100 vs. A w/o		-	0.3500	
Change from Pretreatment to Post-treatment				
N	123	124	126	373
Mean ± SD	-1.3 ± 8.8	-2.2 ± 9.7	-2.7 ± 9.5	-2.1 ± 9.3
Range	-26.0 – 22.0	-32.0 – 29.0	-36.0 – 17.0	-36.0 – 29.0
P-value [a]:				
A200 vs. 100		0.9087	-	
A200 vs. A w/o		0.4496	-	
A100 vs. A w/o		-	0.2875	

[a] P-value derived from Wilcoxon signed rank test.
Extracted from Tables 9.3.2 (pretreatment), 9.3.4 (post-treatment), 9.3.6 (change pre-post).

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Blood pressure:

- Only A100 had a statistically significant mean change in diastolic blood pressure from pre-treatment to 10 minutes post-dose which was -3.4 mmHg, p=0.0003.
- The mean **change** from pre-treatment to post-treatment in diastolic blood pressure for A200 was 2.7mmHg, p= 0.0303.
- The mean **change** from pre-treatment to post-treatment in diastolic blood pressure for A100 was 3.0mmHg, p= 0.0162.
- The mean **change** in systolic blood pressure from pre- to post-treatment for A200 was 3.4mmHg, p= 0.0220.
- The mean **change** in systolic blood pressure from pre- to post-treatment for A100 was 4.2mmHg, p= 0.0118

Respiratory rate:

- There were no important changes in the respiratory rates from pre-treatment to 10 minutes post-dose and to post-treatment.

Despite the fact that these changes are statistically significant, none of these changes are clinically relevant.

In **Study ART03-001** the Sponsor proposed to demonstrate the changes in cardiovascular responses following administration of articaine such as 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), and systemic vascular resistance. Another objective was to compare the cardiovascular responses of the two epinephrine containing formulations

The following differences were found in the cardiovascular parameters and vital signs between A200 and A100:

Pulse rate:

- The heart rate at 10 minutes post-dose was 69.6 bpm for A200 and 78.2 bpm for A100. The difference was marginally statistically significant, p = 0.0471.
- The maximum change in heart rate from pre-dose was -3.1 ± 11.2 bpm for A200 and 1.6 ± 17.6 bpm for A100. The difference was statistically significant, p =0.0288.

Blood pressure:

- The systolic blood pressure at 10 minutes post-dose for A200 was 124.8 mmHg and for A100 was 130.6 mm Hg. The difference between them was statistically significant, p=0.0456.
- The mean of the maximum change of systolic blood pressure was -4.5 mmHg for A200 and -5.0 for A100.
- The pre-treatment systolic blood pressure was 121.4 ± 7.7 mm Hg for A200 and 127.2 ± 6.5 mm Hg for A100. The difference was statistically significant, p = 0.0419).

Other cardiovascular parameters:

- The small artery elasticity index at 70 minutes post-dose for A200 was 11.4 ml/mm Hg and A100 for 12.9ml/mm Hg. The difference between the two was statistically significant, p = 0.0357.
- The cardiac output at 10 minutes post-dose for A200 was 6.2 L/min and 6.35 L/min for A100, p = 0.0445 using the Wilcoxon Signed Rank Test.
- The time to maximum change of systemic vascular resistance index from pre-dose for A200 was 74.6 ± 36.0 min. and 52.9 ± 38.7 min for A100, p = 0.0249.

Respiratory rate:

- There were no statistically significant changes in respiratory rates from pre-dose to 10 minutes post-dose.
- The mean change and standard deviation of respiratory rate from pre-dose to post-treatment for A200 was 0.1 ± 0.8 respirations/min and for A100 was -0.5 ± 0.7 respirations/min. The difference between the two was marginally statistically significant, p= 0.047.

Despite the statistically significant differences in heart rate and blood pressure mentioned above those are not clinically relevant.

The following tables summarize the maximum cardiovascular stimulatory responses in Study ART 03-001 (tables provided by the Sponsor, NDA Vol. 28, p. 54-56).

Table 7.1.8.3-5 **Summary of Maximum Cardiovascular Stimulatory Responses in Study ART03-001**

	4% Articaine 1:200,000 Epinephrine	4% Articaine 1:100,000 Epinephrine	P-value for Difference Between Groups
Heart Rate (beats/minute)			
Pre-Dose			
N	13	14	
Mean ± SD	67.2 ± 9.4	69.0 ±14.7	
Maximum Change from Pre-Dose			
N	13	14	
Mean ± SD	-3.1 ± 11.2	1.6 ± 17.6	0.0288[1]
Time to Maximum Change (minutes)			
N	13	14	
Mean ± SD	64.6 ± 45.0	51.4 ± 42.4	0.2619[a]
Systolic Blood Pressure (mmHg)			
Pre-Dose			
N	13	14	
Mean ± SD	124.7 ± 5.0	125.1 ± 6.1	
Maximum Change from Pre-Dose			
N	13	14	
Mean ± SD	-4.5 ± 15.8	-5.0 ± 14.2	0.9225[a]

	4% Articaine 1:200,000 Epinephrine	4% Articaine 1:100,000 Epinephrine	P-value for Difference Between Groups
Time to Maximum Change (minutes)			
N	13	14	
Mean ± SD	77.7 ± 32.4	72.9 ±35.4	0.6410 [a]
Diastolic Blood Pressure (mmHg)			
Pre-Dose			
N	13	14	
Mean ± SD	73.1 ± 3.7	73.1 ± 6.4	
Maximum Change from Pre-Dose			
N	13	14	
Mean ± SD	-5.4 ± 7.4	-7.8 ± 8.1	0.2707 [a]
Time to Maximum Change (minutes)			
N	13	14	
Mean ± SD	73.1 ± 32.8	57.1 ± 30.0	0.1077 [a]
Mean Blood Pressure (mmHg)			
Pre-Dose			
N	13	14	
Mean ± SD	90.3 ± 2.5	90.4 ± 5.8	
Maximum Change from Pre-Dose			
N	13	14	
Mean ± SD	-3.5 ± 9.2	-5.8 ± 8.6	0.4796 [b]
Time to Maximum Change (minutes)			
N	13	14	
Mean ± SD	55.4 ± 29.6	56.4 ± 33.7	0.8702 [a]
Stroke Volume (cc/beat)			
Pre-Dose			
N	13	14	
Mean ± SD	86.8 ± 12.6	85.6 ± 14.1	
Maximum Change from Pre-Dose			
N	13	14	
Mean ± SD	8.7 ± 12.3	2.7 ± 15.8	0.1415 [a]
Time to Maximum Change (minutes)			
N	13	14	
Mean ± SD	56.9 ± 39.9	42.9 ± 27.0	0.1164 [a]
Cardiac Output (L/min)			
Pre-Dose			
N	13	14	
Mean ± SD	5.9 ± 0.5	5.9 ± 0.3	
Maximum Change from Pre-Dose			
N	13	14	
Mean ± SD	0.1 ± 0.9	-0.1 ± 0.9	0.6934 [a]

	4% Articaine 1:200,000 Epinephrine	4% Articaine 1:100,000 Epinephrine	P-value for Difference Between Groups
Time to Maximum Change			
N	13	14	
Mean ± SD	62.3 ± 46.6	60.7 ± 42.7	0.9377 [a]
Large Artery Elasticity Index (mL/mmHg)			
Pre-Dose			
N	13	14	
Mean ± SD	18.6 ± 5.7	17.9 ± 4.8	
Maximum Change from Pre-Dose			
N	13	14	
Mean ± SD	2.9 ± 10.6	3.3 ± 8.5	0.9569 [a]
Time to Maximum Change (min)			
N	13	14	
Mean ± SD	63.1 ± 35.2	75.7 ± 35.2	0.5517 [a]
Small Artery Elasticity Index (mL/mmHg)			
Pre-Dose			
N	13	14	
Mean ± SD	11.7 ± 2.7	11.1 ± 3.8	
Maximum Change from Pre-Dose			
N	13	14	
Mean ± SD	1.2 ± 5.7	1.3 ± 8.2	0.9206 [a]
Time to Maximum Change (minutes)			
N	13	14	
Mean ± SD	50.0 ± 33.9	54.3 ± 38.4	1.0000 [a]
Systemic Vascular Resistance (dynes–s-cm5)			
Pre-Dose			
N	13	14	
Mean ± SD	1227.5 ± 97.0	1248.7 ± 123.7	
Maximum Change from Pre-Dose			
N	13	14	
Mean ± SD	-10.1 ± 202.3	-48.9 ± 273.4	0.7667 [a]
Time to Maximum Change (minutes)			
N	13	14	
Mean ± SD	74.6 ± 36.0	52.9 ± 38.7	0.0249 [a]

[a] p-value for differences between treatment groups determined using Student's t test.
[b] pvalue for difference between treatment groups determined using Signed rank test where test for normality failed.
Extracted from Tables 6.1, 6.2, 6.3 (heart rate), 7.1, 7.2, 7.3 (systolic blood pressure), 8.1, 8.2, 8.3 (diastolic blood pressure), 9.1, 9.2, 9.3 (mean blood pressure), 10.1, 10.2, 10.3 (stroke volume), 11.1, 11.2, 11.3 (cardiac output), 12.1, 12.2, 12.3 (large artery elasticity index), 13.1, 13.2, 13.3 (small artery elasticity index), and 14.1, 14.2, 14.3 (systemic vascular resistance).

7.1.8.4 Additional analyses and explorations

None were performed by the Sponsor or by the reviewer.

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

ECG testing was not included by the Sponsor in the development program, nor was it requested by the Division. The primary justification for this course of action was the limited systemic exposure to the study drug product. Data from the previously approved formulation of 4% articaine and 1:100,000 epinephrine indicated that there was no reason to expect any adverse effect in the ECG. Cardiovascular parameters like ECG, QT prolongation and blood pressure were measured in the dog in 4-week toxicity studies. No changes in these parameters were seen up to 80 mg/kg/day.

7.1.9.2 Additional analyses and explorations

None were performed by the Sponsor or by the reviewer.

7.1.10 Immunogenicity

Not applicable to this NDA.

7.1.11 Human Carcinogenicity

The sponsor was not required, according to ICH M3 guidance, to conduct carcinogenicity assessments for lidocaine or epinephrine as they are not to be used continuously for >6 months.

7.1.12 Special Safety Studies

Special safety studies were neither proposed by the Sponsor nor requested by the Division.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

There is no known abuse potential for articaine HCl.

7.1.14 Human Reproduction and Pregnancy Data

The Sponsor did not conduct reproductive and developmental toxicology studies for this application.

Articaine HCl is considered a pregnancy category C drug.

From the proposed Septocaine® label "In developmental studies, no embryofetal toxicities were observed when Septocaine® was administered subcutaneously throughout organogenesis at doses up to 40mg/kg in rabbits and 80 mg/kg in rats (approximately 2 times the maximum recommended human dose on a mg/m^2 basis). In rabbits, 80 mg/kg (approximately 4 times the maximum recommended human dose on an mg/m^2 basis) did cause fetal death and increased fetal skeletal variations, but these effects may be attributable to the severe maternal toxicity, including seizures, observed at this dose.

When articaine hydrochloride was administered subcutaneously to rats throughout gestation and lactation, 80 mg/kg (approximately 2 times the maximum recommended human dose on a mg/m^2 basis) increased the number of stillbirths and adversely affected passive avoidance, a measure of learning, in pups. This dose also produced severe maternal toxicity in some animals. A dose of 40mg/kg (approximately equal to the maximum recommended human dose on a mg/m^2 basis) did not produce these effects. A similar study using Septocaine® 100 (articaine hydrochloride and epinephrine 1:100,000) rather than ——— 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."

It is not known if articaine is excreted in human milk.

For further detail, please refer to the pharmacology/toxicology review.

7.1.15 Assessment of Effect on Growth

Given the limited systemic exposure to articaine HCL and the acute nature of its clinical use, assessment of the effect of Septocaine 200 on growth was not required and was not conducted.

7.1.16 Overdose Experience

The overdose potential of articaine HCl in animals and man is discussed in NDA 20-971, Vol. 1.3, Section 8.6.2, p. 276-281 and the toxicity profile and management of overdose with articaine HCl are discussed in the same Section, p.281-282.

7.1.17 Postmarketing Experience

The 4% articaine HCl with 1:100,000 epinephrine formulation has been registered and approved for use in 53 countries, including the United States (FDA approval in 2000) and Canada. The 4% articaine HCl with 1:200,000 formulation has been registered and approved for use in 47 countries, including Canada.

The US formulation of 4% articaine HCL, which does not contain EDTA, has received marketing approval in Great Britain (1998, 1:100,000 and 1:200,000 formulations), United States (2000, 1:100,000 formulation) and Australia (2004, 1:100,000).

The Sponsor submitted data collected from regulatory authorities worldwide on the number of doses sold and the number of adverse events reported (NDA Vol. 28, Section 7.7 Post-Marketing Safety Surveillance, p.176). For 4% articaine HCl with 1:100,000 epinephrine, there were ——— cartridges sold between 1998 and 2004 and there were 247 adverse events reported for the same period. For 4% articaine HCl with 1: 200,000 epinephrine there were ——— doses sold from 1998 through 2004 and there were 90 adverse events reported for the same period. For a listing of the adverse events reported to the worldwide regulatory authorities please refer to Section 10.2 Listings of Adverse Events.

A search performed in AERS by this reviewer, using only the term "articaine" since approval, resulted in 33 case reports> Most of the reports provide scant narrative details. The most common adverse events were related to the nervous system, in particular hyposthesias and

paresthesias but also included convulsions, dizziness. Other adverse events that were mentioned only once but were clinically relevant were angioneurotic edema, drug hypersensitivity, dysgeusia and hypogeusia, syncope, palpitations, mucosal erosion, impaired healing.

Another search performed in AERS by the Office of Drug safety which included not only the term "articaine" but included a search of combination products containing articaine and epinephrine resulted in 158 cases. This search also revealed a higher frequency of adverse events related to the nervous system which included paresthesia and hypoesthesia, neuralgia, nerve injury, burning sensation, facial palsy. Other adverse events that constituted single listings but are of clinical relevance were gingival erosion, oral mucosal exfoliation.

The profile of the adverse events found in the searches conducted does not differ from what is known of articaine. For a listing of the adverse events found in the AERS search refer to Section 10.2 Listings of Adverse Events.

The only death was a foreign case of a 58 year old female, who died due to multi-organ failure secondary to Stevens Johnson Syndrome, following treatment with midazolam for sedation. There were other suspect drugs besides articaine: ketoprofen, quinidine hydrogen sulphate, penicillin. There is no reason to believe that articaine was the causative drug of this adverse event.

There was one foreign pediatric case of a 6 year old who received midazolam, ketamine, and articaine with epinephrine 1:200,000 prior to having a tooth filled. The patient had a convulsion, increase in body temperature and was hospitalized.

The label of the currently approved formulation addresses paresthesias by listing it in the section Adverse Reactions, where it informs a 1% incidence in the clinical trials that were held in the initial submission. The label also makes reference in the section Precautions- Information for Patients that "The patient should be informed in advance of the possibility of temporary loss of sensation and muscle function following infiltration and nerve block injections".

A report in the literature by Finesterer et al describes the case of a 28 year-old woman who presented worsening of manifestations of Kearns-Sayre syndrome after receiving 60mg articaine and 0.009mg epinephrine (1.5ml Ultracaine Dental Forte). Kearns-Sayre syndrome is a mitochondrial myopathy, in the case of this patient due to a 5.9-kb deletion of mitochondrial DNA. The patient experienced an adverse reaction immediately after an inferior mandibular injection. She developed a feeling of heat progressive fatigue, bradyphrenia, weakness, and increased desire to sleep, inappetence, frequent urination; respiratory and bulbar muscles were unaffected. The following day she consulted her neurologist and she presented diffuse weakness, reduced tendon reflexes, and subclonic Achilles tendon reflexes. She recovered 48 hours after the injection.

Another case report by El-Qutob et al describes a case of a 51year-old woman who had an immediate skin reaction after subcutaneous administration of articaine before a dental procedure

which was confirmed by skin testing. Despite testing positive for articaine her skin prick test was negative for lidocaine, mepivacaine and bupivacaine.

In a series reviewed by Hillerup and Jensen, fifty-four injection injuries in 52 patients were caused by mandibular block analgesia affecting the lingual nerve (n=42) and/or the inferior alveolar nerve (n=12). Mandibular block caused lingual injury more frequently than inferior alveolar nerve injury. Unlike most mechanical injuries after surgery, injection injuries were not followed by a course of spontaneous improvement of neurosensory and/or gustatory function. Fifty-four percent of the nerve injuries were associated with articaine 4%, and the authors claim a substantial increase of injection injuries followed its introduction in Denmark.

The foreign labels have been requested from the Sponsor and were sent too late in the cycle for inclusion in the review.

A consult to the Office of Drug Safety has been requested to compare the incidence of paresthesias and hypoesthesias between 4% articaine and epinephrine and lidocaine for dental use. This consult is pending at the time of this review.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

The table 4.2-1 summarizes the human subject trials conducted in support of this application.

A total of 182 patients were enrolled in the 4 trials. One subject withdrew consent in each one of the studies -ART02-001, ART02-002 and ART03-001- all of them after one treatment with A100. According to the Sponsor, none of the patients withdrew because of an adverse event.

Each subject/ patient was exposed to the different formulations as displayed in the table below.

Table 7.2.1.1-1 **Extent of Exposure of Articaine** (table created by the reviewer)

	A100	A200	Aw/o	Doses
ART02-001	63	62	62	1.7 ml
ART02-002	63	62	62	1.0 ml
ART02-003	42	42	-	1.0-6.8 ml*
ART03-001	14	13	-	11.9 ml
Total	182	179	124	-

* ART 02-003- 11visits ~ 1 cartridge, 46 visits ~ 2 cartridges, 22 visits ~ 3 cartridges, 5 visits ~ 4 cartridges.

7.2.1.2 Demographics

The table below summarizes the gender, race, and ethnicity of the population studied. The Sponsor did not provide a database with all the subjects with a listing of all the ages (Sponsor provided a list of dates of birth instead). The table below was created by the reviewer with information from the individual studies.

Table 7.2.1.2-1 Summary of the Demographics for All Studies

Demographic	Demographic subgroup	Total subjects/patients treated
Gender	Male	103
	Female	79
Race	White	129
	Black or African-American	24
	Asian	14
	Native Hawaiian or Other Pacific Islander	0
	American Indian or Alaska Native	0
	Other	8
	Missing information	4
Ethnicity	Hispanic	13
	Non-Hispanic	155

There is a predominance of male subjects over female subjects, and an unbalanced distribution among races with predominance of Whites. Among the ethnic groups, there was a predominance of Non-Hispanics over Hispanics. No relevant conclusions could be made for other racial groups.

Since a dataset with the listing of all the ages is not available at this time, this reviewer concluded by analyzing the individual studies that:

- In Studies ART 02-001 and ART 02-002 there were no patients > 57 years old and the patients were predominantly 18 to 26 years of age.

- In Study ART02-003 approximately 80% of the 42 patients enrolled were between 40 and 59 years old. Only one patient was 65 years of age.
- In Study ART03-001 (which was the study where subjects were exposed to the maximum recommended dose) there were mostly young adults, between 24-38 years old and only two of them were actually > 30 years old.

7.2.1.3 Extent of exposure (dose/duration)

This drug is for single application. The doses studied were 1.7ml of anesthetic for mandibular block injection, 1.0ml for maxillary infiltration and up to 6.8ml for complex procedures. Study ART03-001 provided safety and tolerability data for 11.9 ml which is the maximum recommended dose. In clinical practice, dentists sometimes use extra doses for maxillary infiltration and mandibular blocks. No data has been generated to support multiple dosing of this product for these anesthesia techniques, especially in the event of anesthetic failure which was particularly high for mandibular nerve block in ART 02-001.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

No other studies other than those described above were submitted for the evaluation of safety.

7.2.2.2 Postmarketing experience

The Sponsor provided a listing of adverse events reported by regulatory authorities worldwide between 1998 and 2004. In addition, there were 33 cases in the AERS. The assessment of adverse events using these sources is discussed in section 7.1.17 Postmarketing Experience.

7.2.2.3 Literature

A literature review was provided by the Sponsor and summarized in a table format. A PubMed search done by this reviewer found the same studies except for a few more recent articles that probably had not yet been published by the time the Sponsor submitted the NDA.

One article by Hillerup and Jensen, reviewed 54 injection injuries in 52 patients caused by mandibular block analgesia affecting the lingual nerve (n=42) and/or the inferior alveolar nerve. Mandibular block analgesia caused lingual nerve injury more frequently than inferior alveolar nerve injury. Injection injuries were not followed by a course of spontaneous improvement of neurosensory and/or gustatory function. Fifty-four percent of the nerve injuries were associated with articaine 4%, and a substantial increase in the number of injection injuries followed its introduction into Denmark.

An article by Finsterer et al describes a severe adverse reaction to local anesthesia with articaine for tooth extraction in a 28-year-old woman with Kearns-Sayre syndrome due to a 5.9-kb mitochondrial DNA deletion. The patient was subjected to local anesthesia with 1.5 mL (60 mg) articaine in the left submandibular nerve for tooth extraction. Five minutes after the injection the patient developed weakness of the limb muscles, extreme fatigue, somnolence, a feeling of heat, lack of appetite, and frequent urination. The adverse reaction resolved spontaneously within 48 hours without sequelae.

Another report by El-Qutob et al reported the case of a 51-year-old woman who had an immediate skin reaction after subcutaneous administration of a local anesthetic of articaine and epinephrine before a dental procedure.

7.2.3 Adequacy of Overall Clinical Experience

Considering that this is a supplement to the original NDA 20-971, a great deal of information had already been provided previously. This clinical program had the following objectives:

- To demonstrate that the 4% articaine formulation with 1:200,000 epinephrine was non-inferior to the approved articaine product.
- To characterize the anesthetic properties of the new formulation.
- To demonstrate that the 4% articaine formulation with 1:200,000 epinephrine is a safe product.
- To demonstrate that the two formulations have different hemostatic properties.

The population size had been discussed with the Agency, and was agreed upon (meeting minutes April 30, 2002). Despite the small population studied, and the shortcomings mentioned in the review, the Sponsor succeeded to demonstrate what was proposed.

This submission did not provide additional information for subpopulations (races, geriatric and pediatric population), patients with underlying conditions and on medications (drug-drug interactions).

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

The Sponsor provided two publications describing the effect of Septocaine on local tissue reaction and wound healing in rodents.

In the first study, 4 groups of rats were subjected to different treatments: 2% lidocaine with 1:100,000 epinephrine, 4% articaine with 1:100,000, saline and surgical incision only. The surgical wounds were sutured with non-absorbable silk and no antibiotics were used. On the seventh day all rats were killed. The wound healing was measured and samples were sent for histology and for breaking strength test (BST). According to this study, both lidocaine and articaine delayed wound healing when compared to that of the control group. The histology and BST results demonstrated that lidocaine had better efficacy in wound healing when compared to that of the articaine group (Dogan N, Ucok C, Korkmaz C, et al. The effects of articaine hydrochloride on wound healing: an experimental study. *J Oral Maxillofac Surg.* 2003; 61(12): 1467-70).

A second study looked at local tissue reaction. Rats received subcutaneous implants which contained: 2% lidocaine without vasoconstrictor, 0.5% bupivacaine solution with 1:200,000 epinephrine, 4% articaine and 2% mepivacaine both with 1:100,000 epinephrine and 0.9% sodium chloride solution as a control. Animals were sacrificed at 1, 2, 5, and 10 days. Histological evaluation revealed that bupivacaine caused the most intense inflammatory reaction, articaine and mepivacaine generated similar inflammatory reaction, and lidocaine caused the least intense inflammatory reaction. These results suggest that the anesthetic solutions that contain vasoconstrictors are more irritating to the tissues, and consequently may be the cause of post anesthetic pain (Ribeiro PD, Sanches MG, Okamoto T. Comparative analysis of tissue reactions to anesthetic solutions: histological analysis in subcutaneous tissue of rats. *Anasth Prog* 2003; 50(4): 169-80).

The pharmacology/ toxicology reviewer felt that the human risk is minimal. For further details please refer to the pharmacology/toxicology review.

7.2.5 Adequacy of Routine Clinical Testing

Routine clinical testing was limited to vital sign collection and cardiovascular measures. The timing of the vital signs assessments was important as these were the only quantitative assessments that could be related to systemic absorption of epinephrine. The vital signs were collected to detect the effects of the study drug. In Studies ART02-002, ART02-003 and ART03-

001 an additional set of vital signs at 5 minutes post-dose might have been informative by providing information on the immediate effects of epinephrine, especially in the cases where positive blood aspiration into the syringe occurred.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Metabolism, clearance and interaction of articaine and epinephrine were not studied by the Sponsor and were not required by the Division for this application. Knowledge of these processes from the approved articaine product containing epinephrine should be applicable.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

As mentioned in Section 7.1.5.1 Eliciting adverse events data in the development program, the Sponsor did not elicit specific side effects that could have been related to the anesthetic and epinephrine such as sleepiness, drowsiness, grogginess, lethargy, lightheadedness, seizures, tingling or numbness in other locations of the body besides the oral area.

7.2.8 Assessment of Quality and Completeness of Data

As of the time of this review the Sponsor has not yet submitted a complete, integrated, safety database as requested. The data analysis conducted for this review was based on data from the individual studies.

There were no integrated datasets with the patients' demographics.

7.2.9 Additional Submissions, Including Safety Update

No additional safety data was submitted.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

There were no deaths and there were no serious or life-threatening adverse events in the clinical trials.

The studies compared two drug formulations with epinephrine among themselves and two of the studies had an additional arm with the same anesthetic without epinephrine. In all the studies, the adverse events had a similar profile and no unexpected adverse events were detected. However one must take into consideration the small number of the population studied. In addition the representation of all races was very uneven as well as the age distribution.

Paresthesias occurred at a rate of 3 over 182 treatments (1.6%). Two of them occurred in the A100 group, one following a mandibular block and the other following a surgical procedure where several injections were given at once. Another case occurred in the A200 group following a maxillary infiltration.

The adverse events obtained in this reviewer's AERS search revealed that 18 of the 33 cases reported (54%) occurred in patients >40 years of age (<16 years- 1 case; 17-30 years, 2 cases; 31-50 years, 14 cases; 51-70 years, 9 cases; >71 years 2 cases).

Drug interactions with common drugs used in the adult and geriatric population was not addressed by the studies. The geriatric population was excluded from the clinical trials.

The pediatric population was also excluded from the clinical studies submitted. For further detail please refer to the Section 8.4 Pediatrics.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

The Sponsor did not provide an integrated dataset for all the studies combined. Instead, some data from Studies ART02-001 and ART02-001 were combined because of the similarity of their study design. The data from Studies ART02-003 and ART 03-001 were presented individually.

7.4.1.2 Combining data

As of the time of this review, an integrated safety database had not been provided by the Sponsor. Tables have been created by the reviewer with data from the individual reports. The Sponsor submitted later in the review a dataset that partially integrated information for all the studies.

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

The following table indicates that, overall, adverse events occurred more frequently with higher anesthetic doses (table created by the reviewer with data from the incidence of adverse events in each study).

Table 7.4.2.1-1 **Adverse Events by Dose**

	ART02-001	ART02-002	ART02-003	ART03-001
Dose	1ml	1.7ml	1- 6.8ml	11.9ml
Aw/o	4/62 (2.1%)	17/62 (27.4%)	-	-
A100	7/63 (11.1%)	18/63 (28.5%)	15/42 (35.7%)	12/14 (85.7%)
A200	8/62 (12.6%)	13/63 (20.9%)	12/42 (28.5%)	6/13 (46.1%)

The incidence of adverse events increased with higher doses of anesthetic.

7.4.2.2 Explorations for time dependency for adverse findings

All adverse events occurred within one day of treatment, and most of them resolved within 24 hours. By the time of the final study assessment all adverse events were resolved.

7.4.2.3 Explorations for drug-demographic interactions

An integrated dataset to assess for the correlation the adverse events with the demographics is not available.

7.4.2.4 Explorations for drug-disease interactions

Exploration for drug-disease interactions was not performed since all the studies included mostly healthy subjects.

7.4.2.5 Explorations for drug-drug interactions

Exploration for drug-drug interactions was not performed since the studies excluded patients on a variety of medications and included mostly healthy subjects. A dataset combining the adverse events and concomitant medications that were not in the exclusion criteria was not provided. However, an analysis of the adverse events and the concomitant drugs was performed by the reviewer, and no correlation between the two was found. On the other hand, it would be unlikely to detect a signal within the relatively small population studied.

7.4.3 Causality Determination

The adverse events that were likely related to the 4% articaine with 1:200,000 were headache, pain, trismus, numbness and tingling, positive aspiration of blood into syringe, swelling, burning sensation above injection site, sleepiness. Palpitation occurred in a patient who received the 1:100,000 formulation and vasovagal syncope occurred in a patient who received the formulation without epinephrine.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The Sponsor provided data to support the use of 4% articaine with 1:200,000 at the dose of 1ml for maxillary infiltration, 1.7ml for mandibular block and up to 6.8ml for complex procedures. Pharmacokinetic and safety information was obtained with doses of 11.9ml administered to 14 subjects. There is no data to support re-dosing for the procedures listed above. The data from ART 03-001 supports that doses up to 11.9ml are tolerated and safe when given for multiple simultaneous maxillary infiltrations (0.8ml-1.7ml) and bilateral inferior nerve blocks (1.7ml).

8.2 Drug-Drug Interactions

Drug-drug interactions have not been addressed in this NDA submission. The subjects and patients studied were mostly healthy at screening and excluded patients that were taking medications such as nonselective beta-blockers, monoamine inhibitors, tricyclic anti-depressants, phenothiazine, butyrophenones, vasopressor drugs, ergot-type oxytocic drugs, aspirin, acetaminophen, non-steroidal anti-inflammatory drugs, opioids or any other analgesics and pre-sedative medications. An analysis performed by the reviewer did not find a correlation between the adverse events reported and any concomitant medications. The concomitant medications were mostly oral contraception drugs, allergy medications, antidepressants among others and a few patients were taking anti-hypertensive drugs, thyroid hormone, insulin and stimulant.

8.3 Special Populations

The data submitted does not allow for conclusive dosing recommendations by gender, race or age due to the small number patients in the program and the uneven distribution of the patients enrolled. The geriatric population and individuals with cardiac, hepatic and renal impairment were not included in the studies; consequently, specific recommendations for these populations cannot be made. The pediatric population was not included in this clinical program; therefore, no new labeling information is available.

8.4 Pediatrics

Septocaine® was approved for use in children 4 years and above. The approval for use in children was based on data from studies conducted by the Sponsor in which 50 children, 4 to 13 years of age received Septocaine ® (the formulation with 1:100,000 epinephrine) for simple procedures (N=43) and complex procedures (N=7). Twenty children received 2% lidocaine hydrochloride with 1:100,000 epinephrine. In addition the Sponsor provided literature evidence to support the safety profile of articaine. The adverse events were reported for 4 of the patients (8%): accidental injury, headache, injection site pain, pain). Only one of them was considered related to the study drug (accidental lip injury). For further detail please refer to the pediatric data submitted in NDA 20-971, Vol. 1.3, Section 8.2.3, p. 183-192 and Section 5.1 Pharmacokinetics, of this review.

From the Approvable Action Memorandum, January 13, 1999: "As described, there has been adequate evaluation of the safety of articaine in over 1000 patients and subjects (all but 50 of whom were given the US formulation) with only minor adverse events reported. The development program also included adequate numbers of children as young as 4 years of age (Local anesthesia for children younger than 4 years is not a generally recommended practice for dental procedures). The number of pediatric patients in the less 4-13 year age group prospectively studied in this NDA was limited. However reports using the European formulation in 66 children from 4 to 6 years of age, confirmed the expected profile of few adverse events. The pharmacokinetics of articaine in the pediatric population, as noted by Dr. Doddapaneni, does not differ significantly from the adult, and contributes to the review team's assessment that the product should perform similarly in children, both in terms of efficacy and safety. There were no serious or life-threatening adverse events reported in this NDA."

A letter was sent to the Sponsor on November 23, 2005, requesting the submission of a pediatric development plan within 120 days and the submission of the pediatric studies was deferred until December 31, 2008. The Sponsor replied to the letter stating that they believe the pediatric requirement was fulfilled with the approval of Septocaine® in 2000.

According to further discussion with the Division of Pediatric Drug Development this submission does not trigger PREA because its submission predates April 1, 1999. However, the Sponsor should be encouraged to submit a Proposed Pediatric Study Request (PPSR).

8.5 Advisory Committee Meeting

Not applicable since this drug product has not been the subject of any advisory committee meeting.

8.6 Literature Review

A search in PubMed did not result in any additional literature information that would have impacted the review of this product.

8.7 Postmarketing Risk Management Plan

Because there is minimal risk of abuse with local anesthetics, and the use of this product is limited to clinical settings by healthcare providers, a Postmarketing Risk Management Plan was neither required nor submitted.

8.8 Other Relevant Materials

In addition to the data and literature submitted by the Sponsor, the Action Package of the original NDA application was reviewed.

The Division of Dermatology and Dental Drug Products was consulted to assess the adequacy of the endpoints chosen and to address specific dentistry questions.

The Office of Medication Errors and Technical Support was consulted to assess the proprietary names proposed.

The Office of Drug Safety was consulted and to assess the incidence of paresthesias of articaine and compare to that of lidocaine after dental use of the anesthetics and it is pending at the time of this review.

Other information sources utilized in this review were:

- Response to Request for Additional Information, dated December 21, 2005 (clarification on status of pediatric studies, detailed indexing of the volumes, electronic SAS transport file data)
- Response to Second Request for Additional Information, dated December 27, 29,2005 (clarifications on protocol violations, data clarifications, bibliographical references)
- Financial Disclosure by Clinical Investigators, dated January 23, 2006
- Response to Third Request for Additional Information, dated February 3, 2006 (clarifications about the EPT procedure, rationale for the disparity in the rate of success in anesthesia among the study centers, rationale for the anesthetic dose used in Study ART 02-002, investigator assignments to each patient)

- Response to Request for Additional Information, dated February 10, 2006 (CRF for subjects and patients that withdrew from the studies, data clarifications and tables of adverse events using COSTART terms)
- Response to Request for Foreign Package Insets, dated February 21, 2006 (the Sponsor submitted the Canadian, French, British and German labels, with translations)
- Response to Request for Additional Information, dated March 9, 2006 (the Sponsor submitted data on the subject descriptive ratings for studies ART 02-001, ART 02-002, ART 02-003 and ART 03-001)

9 OVERALL ASSESSMENT

9.1 Conclusions

This supplemental NDA comes in as a second cycle for the NDA 20-971. Two articaine products containing different epinephrine concentrations were filed in 1998 under NDA 20-971. Only the formulation with 1:100,000 was approved on April, 2000. After discussions with the Division about the clinical study design, the Sponsor now submits clinical studies to support the approval of the other formulation.

The clinical program consisted of four studies. Two of them, ART02-001 and ART02-002, were non-inferiority trials comparing the efficacy of the two formulations with epinephrine and also compared them to articaine without epinephrine. The two studies had similar design but differed in the doses used and anesthetic technique (inferior mandibular block in the first study and maxillary infiltration in the second study). The efficacy rates differed widely in the first study across the study centers.

Overall the Sponsor succeeded to demonstrate that:

- The formulation with epinephrine 1:200,000 is not inferior to the formulation with epinephrine 1:100,000 in achieving EPT-assessed profound anesthesia following inferior mandibular block.
- The formulations with epinephrine are both superior to articaine alone in achieving EPT-assessed profound anesthesia following inferior mandibular block.
- The addition of epinephrine did not affect the time of onset of any of the three formulations, following inferior mandibular block. All three formulations had similar time to onset.
- The addition of epinephrine resulted in prolonged duration of anesthesia for A100 and A200 compared with Aw/o, following inferior mandibular block.
- The A200 formulation is not inferior to the A100 formulation in achieving EPT-assessed profound anesthesia following maxillary infiltration.

- The formulations A100 and A200 are both superior to Aw/o in achieving EPT-assessed profound anesthesia following maxillary infiltration.
- The addition of epinephrine did not affect the time of onset of any of the three formulations, following maxillary infiltration. All three formulations had similar time to onset.
- The addition of epinephrine prolonged the EPT-assessed duration of anesthesia for A100 and A200 compared with Aw/o, following maxillary infiltration. The formulations A100 and A200 lasted longer than the Aw/o.

The third study, ART 02-003, was designed with the purpose of demonstrating a difference in the hemostatic properties of both formulations containing epinephrine. The Sponsor succeeded to demonstrate better visualization of the surgical field when using 4% articaine with 1:100,000 epinephrine and this is a characteristic that allows differentiating the two formulations.

The fourth study, ART 03-001, was a PK study in which the subjects were exposed to the maximum recommended dose of articaine with the two epinephrine concentrations. The Sponsor demonstrated that the pharmacokinetics of the two drugs are similar.

All the studies provided safety information. There were no unexpected adverse events. Given what is known about articaine from all the clinical trials performed and the marketing experience of formulations with epinephrine 1:100,000 and epinephrine 1:200,000, the articaine formulation with epinephrine 1:200,000 appears to have a favorable benefit-risk ratio.

9.2 Recommendation on Regulatory Action

This reviewer recommends the **approval** of Septocaine — based on the following:

- The Sponsor demonstrated that 4% articaine with 1:200,000 epinephrine is not inferior to the approved articaine formulation with 1:100,000 epinephrine.
- The Sponsor characterized the anesthetic properties of 4% articaine with 1:200,000 as requested by the Division.
- The Sponsor demonstrated that the safety profile of 4% articaine with 1:200,000 epinephrine is similar to the approved articaine formulation with 1:200,000 epinephrine and there are no safety concerns that would preclude the approval of this drug product.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

None required.

9.3.2 Required Phase 4 Commitments

9.3.3 Other Phase 4 Requests

No requests for a phase 4 study are made at this time.

9.4 Labeling Review

The review of the product label has been deferred to interdisciplinary discussions within the Division. A consult to the Office of Drug Safety to address the adequacy of the names suggested by the Sponsor, Septocaine — and Septocaine — , is pending. The names are misleading in the sense that practitioners may think that the designation "— " corresponds to a higher concentration of epinephrine than the " — " formulation when in reality it refers to the more dilute concentration of epinephrine.

9.5 Comments to Applicant

There are no comments to be conveyed to the applicant at this time.

10 APPENDICES

10.1 Review of Individual Study Reports

10.1.1 Study ART-02-001: "The efficacy and clinical anesthetic characteristics of 4% articaine HCL with 1:200,000 epinephrine, 4% articaine HCL with 1:100,000 epinephrine, and 4% articaine HCL without epinephrine, when administered for inferior alveolar nerve block anesthesia"

10.1.1.1 Overall Summary of Findings

The Sponsor conducted a randomized, double-blind, active-control, cross-over, multicenter, phase 3 study seeking to demonstrate the equivalence in anesthetic efficacy between 4% articaine HCL with 1:200,000 epinephrine (A200) and previously approved 4% articaine HCL with 1:100,000 epinephrine (A100). The Sponsor also proposed to compare the anesthetic characteristics (time of onset and duration) between the two formulations containing epinephrine and the unapproved product, 4% articaine alone (Aw/o).

Sixty-three subjects were randomized to one of six treatment sequences, so that all were exposed to each of the drug formulations over three treatment visits. The mandibular canine tooth on either side was tested with an electric pulp tester (EPT) at each visit to obtain a baseline measure and was retested every 30 seconds up to 10 minutes following an inferior alveolar nerve block with 1.7mL of study drug.

The Sponsor demonstrated that articaine 4% with epinephrine 1:200,000 was equivalent to articaine 4% with epinephrine 1:100,000 in that there was no statistically significant difference in the number of subjects who successfully achieved profound anesthesia within ten minutes following injection of the two drugs (A200 - 54.8% success rate vs. A100 - 47.6% success rate; $p= 0.2253$). The Sponsor also demonstrated that the addition of epinephrine to articaine improved efficacy, i.e., increased the success rate of producing profound anesthesia following mandibular block, for both formulations containing epinephrine compared to the articaine alone (A200 54.8% vs. Aw/o 25.8%, $p < 0.0001$, A100 47.6% vs. Aw/o 25.8%, $p< 0.0001$). However, there was no difference in the time to onset and duration of anesthesia for any of the three formulations.

10.1.1.2 Study Plan

The original version of this protocol was dated June 6, 2003. Sixty-three subjects underwent dental anesthesia at three study sites (21 subjects at each site)- University of Pittsburgh School of Dental Medicine, University of Pennsylvania School of Dental Medicine and The Forsyth Institute- during the period of December 8, 2003 to May 1, 2004. There were no protocol amendments to this study. Source: NDA submission, Appendix 10.1.1., Vol. 15, p. 221.

10.1.1.3 Objectives

The protocol-specified objectives of the study were:

Primary Objective: Demonstrate the equivalence in anesthetic efficacy between the investigational formulation of 4% articaine HCL with 1:200,000 epinephrine as compared to 4% articaine HCL with 1:100,000 epinephrine.

Secondary Objectives:
1. Compare the time to onset of anesthesia and duration of profound anesthesia between 4% articaine HCL with 1:200,000 epinephrine to 4% articaine HCL with 1:100,000 epinephrine, following inferior alveolar block anesthesia.
2. Demonstrate that the addition of epinephrine to 4% articaine solutions improves efficacy of anesthesia following administration of an inferior nerve block injection compared to the formulation with articaine alone.
3. Compare cardiovascular responses observed following administration of the three formulations.

10.1.1.4 Study Design

This was to be a randomized, double-blind, active controlled, cross-over, multicenter, phase 3 study, designed to compare clinical efficacy and anesthetic characteristics of 4% articaine HCl with 1:200,000 epinephrine (A200), 4% articaine HCl with 1:100,000 epinephrine (A100), and 4% articaine HCl without epinephrine (Aw/o), when injected intraoral to induce inferior alveolar nerve block anesthesia.

One ml of A200 was to provide 40 mg of articaine hydrochloride and 0.005 mg of epinephrine base, similarly, 1 ml of A100 was to provide 40mg of articaine hydrochloride and 0.010mg of epinephrine base, and 1 ml of the Aw/o contained only 40mg of articaine hydrochloride.

A total of 63 subjects were to be enrolled and randomized to one of six sequence groups based on a Latin Rectangle design. The sequence groups for study drug were as follows:

- Group 1: A200, A100, Aw/o
- Group 2: A100, Aw/o, A200
- Group 3: Aw/o, A200, A100
- Group 4: A200, Aw/o, A100
- Group 5: A100, A200, Aw/o
- Group 6: Aw/o, A100, A200

10.1.1.5 Efficacy Endpoints

Primary Efficacy Endpoint: The success rate of subjects with complete anesthesia, defined as an EPT value of ≥ 80, following intraoral administration of test drug for inferior alveolar nerve block anesthesia.

Secondary Efficacy Endpoints:

1. Comparison of time of onset and time of duration of anesthesia of the two epinephrine containing formulations by measuring changes in sensory threshold of the dental pulp following electric tooth stimulation.
2. Time of onset and time of duration of anesthesia of the two epinephrine containing formulations compared with the articaine formulation not containing epinephrine determined by measuring changes in sensory threshold of the dental pulp following electric tooth stimulation.

10.1.1.6 Population

The subjects were 63 volunteers in good general health, of both genders, between 18 and 65 years of age inclusive. One subject withdrew consent. The following were the inclusion and exclusion criteria for the study population.

Inclusion Criteria

1) Subjects had to be between 18 and 65 years of age.
2) Females of child bearing potential had to have a negative urine pregnancy test and were to be using adequate means of birth control (abstinence, oral contraceptive steroids, intrauterine device, etc.) for at least one month prior to study entry and during the study.
3) The subjects were to sign the informed consent prior to initiation of any study procedures. The subject had to be able to understand and agree to cooperate with study requirements.

4) The subjects had to have at least one mandibular canine with normal pulp vitality (determined by EPT testing of 10 - 50 units), free of gross caries, and without dental restorations including full coverage (crowns or "caps").

Exclusion Criteria

1) Any known or suspected allergies or sensitivities to sulfites or amide-type local anesthetics or any of the ingredients in the test solutions.
2) Significant history of cardiac or neurological diseases.
3) Severe or frequent cardiac arrhythmias.
4) Treated or untreated hypertension equal to or greater than 140 mm Hg systolic or 90 mm diastolic.
5) Severe or currently symptomatic bronchial asthma.
6) In the investigator's opinion, the subject was considered an inappropriate candidate for the study due to a concomitant medical or psychiatric condition.
7) The subject had evidence of soft tissue infection near the proposed injection site.
8) The subject was taking nonselective beta-blockers, monoamine oxidase (MAO) inhibitors, tricyclic anti-depressants, phenothiazine, butyrophenones, vasopressor drugs or ergot-type oxytocic drugs.
9) The subject had taken aspirin, acetaminophen, non-steroidal anti-inflammatories (NSAIDS), opioids or other analgesic agents within 24 hours of administration of study medication.
10) The subject had taken an investigational drug(s) or participated in another study within four weeks prior to initiation of treatment.
11) Female subject who was lactating or pregnant.
12) The subject required sedative premedication (oral, inhalational, or intravenous) to tolerate the injection procedure.

Subjects could be withdrawn from the study for any of the following reasons:

1) An adverse event(s) that warranted termination as judged by the investigator.
2) The subject decided to withdraw from the study for any reason.
3) The subject required treatment with a prohibited medication.
4) EPT measurements outside of normal range at baseline measurement of each treatment visit.

10.1.1.7 Methods and Procedures

The trial was to have been comprised of 4 visits: a one-hour screening visit and three 4-5 hour treatment visits.

The subjects were to have been screened within 8 days prior to the first treatment visit. At the screening visit, a written informed consent was to be obtained. At that time a complete medical history was to be recorded (including record of all medications taken within two weeks prior to

the screening visit), as well as a brief physical examination of the head, neck and mouth. The test tooth (mandibular canine) was to have been examined to confirm vitality and eligibility. A urine pregnancy test for females was to have been performed at screening and the day of each treatment visit prior to drug administration. The vital signs recorded at the screening visit should have included supine blood pressure, pulse rate, respiratory rate and body weight. With the exception of body weight, all other vital signs were to be measured at the treatment visits prior to administration of the study drug.

During the first treatment visit the patients were to have been randomized to one of the treatment sequence groups described previously in Section 10.1.1.4. Before all treatment visits a urine pregnancy test was to have been repeated for females of childbearing potential. Measurements of the vital signs described above, with the exception of body weight, were to have been performed every five minutes for the entire electric pulp test (EPT) session and at the end of the treatment session.

The inferior alveolar nerve block anesthesia was to have been administered on the same side (left or right) for all treatments. The injection volume was 1.7ml (one cartridge) and it was to have been injected slowly with frequent aspirations over a one-minute time span. According to the sponsor, this is the lowest effective dose of articaine, which was chosen to simulate clinical practice and to avoid high plasma concentrations of anesthetic. No topical anesthetics were to be applied prior to the injection and the local anesthesia technique used was to have been the standard intraoral mandibular injection technique (the sponsor referred to the following reference: Moore, PA, Editor, *Manual of Local Anesthesia in Dentistry, 4th Ed.* , Eastman-Kodak Co, Rochester, NY,1996).

The time of onset and time of duration of anesthesia were to have been determined by measuring changes in the sensory threshold of the dental pulp following electric tooth stimulation using a standard commercially available EPT ([redacted]).

The EPT consisted of a probe that was placed on the midpoint of the incisal third of the labial surface of the mandibular canine tooth on either side, but on the same side for all the three visits. Fluoride gel toothpaste was used to assure the electrode contact. A baseline EPT was obtained at screening and before each treatment visit. The median of three baseline EPT measurements of pulpal sensitivity were determined and recorded prior to the anesthetic administration. Normal baseline EPT sensitivity was considered a value ranging from 10-50. A response to the pulp test is considered a subject sensation, such as pulsation, tingling or pain. The procedure would have been considered successful if the subjects had no sensation to an EPT value of 80 (profound anesthesia), for three times consecutively, no later than 10 minutes after injection. The time from the end of injection, until the time for achieving profound anesthesia was defined as time of onset. The subjects that were successfully anesthetized were further tested with the EPT, every 5 minutes until the initial loss of profound anesthesia was detected. Loss of anesthesia was defined as the re-establishment of any sensation at an EPT of 80, which was confirmed by three consecutive EPT values under 80. All EPTs were to be calibrated before and after study completion. This was the method used by the Sponsor to measure the onset and duration of anesthesia.

The mandibular canine tooth on the anesthetized side of the mandible was the tooth to be monitored throughout the study session. The tooth could not have any dental restorations or gross caries and had to present a normal baseline EPT (sensitivity value 10-50 units) at each treatment visit. The site of tooth contact was the midpoint of the incisal third of the labial surface and to assure the electrode contact fluoride gel was applied to the probe tip.

Onset time for anesthesia was defined as the time (minutes) from completion of the injection (t=0) to the time when profound anesthesia (EPT $\geq$ 80) was established. If profound anesthesia had not been achieved by 10 minutes, the injection was to be considered an anesthetic failure. Duration of anesthesia was the time from establishment of profound anesthesia (onset) to the initial loss of profound anesthesia. Three consecutive tests (at 5-minute intervals) below maximum threshold (EPT = 80) were to be required to assure that the loss of profound anesthesia had occurred.

The median of three baseline EPT measurements of pulpal sensitivity was to have been determined and recorded prior to anesthetic administration. In order to make onset time suitable for continuous analysis, EPT values were to have been determined at 30-second intervals until success (or failure) was obtained. Three consecutive tests (at 30-second intervals) above maximum threshold (EPT $\geq$ 80) were to be required to assure that profound anesthesia had occurred. After this time, testing intervals were to begin again at five or ten minutes post injection and were to be extended to 5 minutes. For example, if onset had occurred at 4 minutes, EPT testing was to have been performed at 0.5, 1, 1.5, 2, 2.5,3, 3.5, 4, 4.5 and 5 minutes and then at 10, 15, 20, 25 minutes, etc., until loss of profound anesthesia was detected.

A descriptive report of anesthetic characteristics was to have been simultaneously elicited. At baseline and immediately following post-injection EPT testing, subjects were to be asked to select one of the following categories of sensory function: 1) no change or alteration in sensation, 2) slight feeling of numbness, 3) moderate but not complete feeling of numbness, and 4) side of my mouth is completely numb. An 8 by 11.5- inch card with these categories was to be presented to the subject to permit rapid selection of their responses.

Adverse events were to have been assessed immediately following the anesthetic testing procedure and at a phone interview 24 hours later. Immediately following the procedure, an investigator assessment would have had included: unexpected pain upon injection, positive aspiration during injection, discomfort at the injection site, swelling at the site of injection (hematoma), rash or other abnormal skin reaction, syncope or any other adverse events that had not been mentioned. At the end of the treatment assessments of adverse events were to have been recorded and the subjects discharged from the sites.

Follow-up procedures would have consisted of an interview by phone call approximately 24 hours after the anesthetic efficacy testing had been completed to determine whether the subject had had any adverse effects after discharge. The investigator or site personnel would have elicited any adverse events by asking the subject whether the subject noticed any changes in his or her health since the previous day testing session. A positive response to this question would

have been followed by other questions regarding location and description of the changes. Also, other likely adverse reactions would have been inquired upon, such as swelling, headache, infection, pain, gingivitis, numbness and tingling. If adverse events occurred, the Adverse Event Form in the CRF was to be completed by the investigator. If the subjects could not be reached at the follow-up call, follow-up information was to be reported as soon as it was received from the subject.

The subject would have completed the study if he or she received three study medications and participated in all follow-up telephone calls. All who received study medication were to have been evaluated for safety.

The following is the study schematic:

Table 10.1.1.7-1 **Study Schematic for ART-02-001 (from the Final Clinical Report, NDA Vol.15, p.37)**

Study Schematic				
Procedure	**Screening Visit[a]**	**Treatment Session 1[b]**	**Treatment Session 2[b]**	**Treatment Session 3[b]**
Informed Consent Signed	X			
Complete Medical History	X			
Brief Physical Exam	X			
Urine Pregnancy Test (females only)	X	X	X	X
Vital Signs	X	X[c]	X[c]	X[c]
Randomization		X		
Study Drug Administration		X	X	X
Drug Accountability		X	X	X
Efficacy Measurement		X	X	X
Adverse Event Assessment[d]		X	X	X
Telephone Follow-up[e]		X	X	X

a. Within eight days prior to the first treatment visit. Screening and Treatment 1 could be done on the same day.

b. One to three weeks after previous treatment visit. Confirmed inclusion and exclusion criteria were met prior to each treatment.

c. Conducted at the following times: prior to administration of study drug (all), five minute intervals for the entire EPT testing session (supine blood pressure and pulse rate only) and immediately following the testing procedure (all). Did not include body weight.

d. Immediately following the testing session.

e. Approximately twenty-four hours following discharge from the site.

10.1.1.8 Analyses Plan

10.1.1.8.1 Analyses of Efficacy

The frequency of successful anesthesia was to have been summarized for the three formulations. A binomial test was to have been used to determine the effect of treatments on success rate. McNemar tests were to have been performed to compare treatment A200 vs. A100, treatment A200 vs. Aw/o, and treatment A100 vs. Aw/o. According to the sponsor, the sites could be pooled together since each treatment had a similar probability of success across all sites and the dentists had all been given injection training to validate the assumption of equal success probabilities.

Time of onset and duration of anesthesia were to have been summarized using means and standard deviations for each of the treatments. If the assumptions of normality had not been met, appropriate normalizing transformations were to be used. The structure of the linear models would have had Treatment (A100, A200, Aw/o) as a fixed factor, Time Period (1 ,2, 3) as a fixed factor, Sequence (1, 2, 3, 4, 5, 6) as a fixed factor, Center (site1, site2, site3) as a fixed factor, and Subject nested in Center x Sequence.

Multiple comparison tests (e.g., Tukey Kramer) were used in the linear model to determine significance between A200 and A100, A200 and Aw/o, and A100 and Aw/o. Multiple comparison tests of the following were performed: treatment A200 vs. A100, treatment A200 vs. Aw/o, and treatment A100 vs. Aw/o. In this case, the likely insignificant difference between