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APPROVAL PACKAGE FOR:

APPLICATION NUMBER
20-971

Medical Review(s)

NDA 20-971
Sponsor: Deproco Inc. 524-C Quigley Blvd., New Castle, DE 19720
Name: Septanest® 1:200,000 and Septanest® — 1:100,000 (4% articaine plus 1/200,000 epinephrine and 4% articaine plus 1/100,000 epinephrine)
Type of Submission: Response to FDA Questions
Proposed Indication: For infiltration and nerve block anesthesia in clinical dentistry.
Reviewer: Harold Blatt, D.D.S.
Team Leader: Bob Rappaport, M.D.
Letter Date by Sponsor: March 22,2000
Date Received by CDER: March 22, 2000
Date Received by Reviewer: March 23, 2000
Date Review Completed: March 28, 1999
CSO: Laura Governale

ADDENDUM TO PRIMARY REVIEW

Background: On January 29, 1999 the FDA issued and Approvable Letter. This submission was made in response to 8 issues/questions raised by the Agency in recent teleconferences.

Indications: For infiltration and nerve block anesthesia in clinical dentistry.

Objectives: The sponsor has provided their response to each issue raised by the Agency as follows:

FDA QUESTION/ISSUE NO. 1

OPDRA is concerned about confusion between Septanest and Citanest and the possible subsequent AE resulting from patient sensitivity to an ingredient found in one drug and not the other.

The sponsor responded:

- On January 21, 1997 the US patent and Trademark Office registered a trademark for Septanest. Astra the makers of Citanest did not file comments in opposition to the name.
- The sponsor feels the names are not pronounced the same way.
- Citanest is marketed as 4% Citanest Plain and 4% Citanest Forte with the Astra logo and using colors black, and black/gold. Septanest proposes to be marketed as Septanest 1:100,000 and [redacted] with the Specialites Septodont logo and the colors blue [redacted]
- The sponsor has been unable to find out if there have been AE associated medication errors in the countries where both products are sold (Canada, France, Holland, Italy, Spain, and the UK). The sponsor has never received any reports of medication errors in the 20 countries where the drug is marketed. *It should be noted that post marketing information on adverse events is generally underreported.*

- Attached to this submission a letter from Dr. ——— This letter states dentists are made aware of possible AEs from local anesthetics in dental school and CE courses, that dentists take extra care to avoid giving the wrong anesthetic because of the fear of malpractice suits, and he has never heard of a foreign dentist confusing the two products.

Originally this reviewer felt that there would not be a problem regarding confusion of the names Citanest and Septanest because of some of the reasons mentioned above by the sponsor. Unfortunately, the sponsor has been unable to provide any new hard data to justify retaining the present name. Therefore, after hearing OPDRA's concerns my tendency is to exercise more caution and now feel that the name should be changed. If, at some time in the future, the sponsor were able to provide new data, this reviewer would be willing to reconsider my opinion.

FDA QUESTION/ISSUE NO. 2

The sponsor submitted a letter from ——— (the cartridge manufacturer) summarizing the imprinting and quality control processes to ensure the printing would not rub off.

This response was satisfactory to the Chemistry Reviewer and Chemistry Team Leader. This reviewer concurs.

FDA QUESTION/ISSUE NO. 3

The sponsor accepts the 505(b)(2) classification.

This is a satisfactory response.

FDA QUESTION/ISSUE NO. 4

The sulfite warnings requested by the Agency will be used on the cartridge, can, box, and package insert. Color copies of the box and can labels with the warning have been attached to this submission.

This response was satisfactory to the Chemistry Reviewer and Chemistry Team Leader. This reviewer concurs.

FDA QUESTION/ISSUE NO. 5

The sponsor has provided the color mock-ups for the cartridge, can, and box labels as requested.

This response was satisfactory to the Chemistry Reviewer and Chemistry Team Leader. This reviewer concurs.

FDA QUESTION/ISSUE NO. 6

The Agency requested copies of sample cartridges, and all labeling and packaging materials for samples if they intend to distribute samples to dentists.

The sponsor responded that they would not distribute samples to dentists. This response is satisfactory.

FDA QUESTION/ISSUE NO. 7

- The sponsor provided two differences between the 1:100, 000 formulation and the 1:200,000 formulation:
    - 1.Duration of anesthesia is longer with the 1:100,000 formulation. They give 6 references for this statement.

This reviewer looked at the references listed below and was unable to make a clear confirmation of the sponsor's assertion that duration of anesthesia was longer with the 1:100,000 formulation.

- *The first two references are correctly quoted from the original NDA (Vol. 1.22, p.7-8, 10.). That the 1:200,000 concentration was chosen for the PK/efficacy study because literature indicates it would have the shortest duration and give the highest plasma levels for articaine and its metabolites for PK analysis.*
- *The reference to Vol. 1.22, p. 37 refers to Vol. 1.64 that contains 48 articles. The sponsor states that, "The studies demonstrate a longer and more consistent duration of anesthesia with the 1:100,000 epinephrine formulations." The reference does not state which articles are summarized from Vol. 1.64.*
- *The sponsor has correctly quoted Vol. 1.40, pp.49-50 as follows: "Increasing the epinephrine concentration from 1:200,000 to 1:100,000 does not appreciably change the latency of analgesia, but appears to provide greater consistency with respect to duration of analgesia." Unfortunately, the quote does not totally agree with the tables in Vol. 40, pp.49-50. The longest duration of anesthesia was found in the Septanest 1:200,000 formulation. The Ultracain and Ubistesin are essentially the same active ingredients (4% articaine) as Septanest(1:200,000) but with a higher concentration of epinephrine(1:100,000). One would normally expect the 1:100,000 concentration to have a longer duration. Also the time to onset (latency period) appears to be longer for the Septanest 1:200,000 compared to the Ultracain and Ubistesin 1:100,000. This is the reverse of what the quote states and what would be expected.[See table on next page.]*

Dose Formulation	*Volume*	*Site of Administration*	*Mean Time to Onset (min.)*	*Mean Duration of Anesthesia (min.)*
4% articaine HCl, 1:200,000 epi (Septanest)	*1.7mL*	*Maxillary infiltration*	*3.65±0.39*	*68.2±8.3*
4% articaine HCl 1:100,000 epi (Ultracain)	*1.7mL*	*Maxillary infiltration*	*1.8±1.2*	*56.7±24.2*
4% articaine HCl 1:100,000 epi (Ubistesin)	*1.7mL*	*Maxillary infiltration*	*2.8±2.8*	*53.7±19.7*
4% articaine HCl, 1:200,000 epi (Septanest)	*0.5mL*	*Vestibular infiltration*	*4.7±1.58*	*54.4±10*
4% articaine HCl, 1:100,000	*0.5mL*	*Vestibular infiltration*	*5.0±2.83*	*66.8±22.7*

[Based on sponsor's Tables Vol. 1.40, pp.49-50.]

- *Vol.1. 64, pp. 171-173 correctly quotes Dr. Malamed's Handbook of Local Anesthesia, "the formulation with 1:100,000 epinephrine provides approximately 75 minutes of pulpal anesthesia; the 200,000 formulation, approximately 45 minutes." However, according to the table above, the duration for 1:100,000 varies from 53.7 minutes to 66.8 minutes and for the 1:200,000 varies from 54,4 minutes to 68.2 minutes. The results appear to be somewhat mixed and unclear.*
- *The sponsor states that in Vol. 1.64, pp.258-269, "the investigators reported longer duration of anesthesia with articaine 1:100,000 than with articaine 1:200,000 epinephrine." This is based on the article by, Ruprecht, S., et al. Schweiz Monatsschr Zahnmed 1991; 101,1286-1290. This study was in 10 healthy male dental school students and was a randomized, double blind crossover study. While this study cannot be considered AWC (no placebo), it does appear that the results are correct. [See table on next page.]*

Solutions	*Start (min.)*	*Duration (min.)*
4% articaine 1;200,00 epinephrine	*4.7± 1.58*	*54.4±22.58*
4% articaine 1;100,000 epinephrine	*5.0±2.83*	*66.8±22.70*

[Based on sponsor's Table II, Vol. 1.64, p.261.]

- 2.The sponsor refers to a letter from Dr. [redacted] that states that the 1:100,000 formulation provides meaningful localized ischemia when minimized bleeding is required during certain dental procedures. He further states that 1:200,000 is preferred by dentists in treating older patients and medically compromised patients (especially cardiovascular patients).

While this reviewer agrees the articaine 1:100,000 epinephrine would be more likely to minimize bleeding in certain dental procedures, the medically compromised and elderly patients can be more safely treated with local anesthetics already on the market that do not contain any epinephrine than by using one that contains 1:200,000 epinephrine.

- In meetings on May 10, 1996 and January 10, 1997, the Agency agreed to the proposed development plan that included a PK/ efficacy study using the 1:200,000 formulation to support approval of both products.

In the May 10, 1996 meeting Dr. Hyman agreed with the rationale of studying the higher strength product to generate safety data. Dr. Hyman noted that the VAS was not a rigorous efficacy measure and that if the sponsor wanted more rigorous data, the level of epinephrine would be important. Dr. Hyman also noted that if the sponsor wanted to make labeling claims regarding quicker onset, deeper anesthesia, shorter duration of anesthesia, or use of less epinephrine, they would have to demonstrate these effects definitively. Dr. Hyman stated, and Dr. [redacted] confirmed, that if the sponsor decided not to make comparative claims (e.g. in advertising) they would not be required to produce additional efficacy data for regulatory approval.

In the January 20, 1997 meeting Dr. [redacted] remarked that if the 20 patient study were not conducted, there would be no study to look at the 1:200,000. Implicit in her statement is that we need further information about that concentration.

- The sponsor stated that the Agency agreed that it is not necessary to test the 1:200,000 formulation for safety.

FDA QUESTION/ISSUE NO. 8

The sponsor responded to a concern regarding the inclusion of a warning about methemoglobinemia in the French label. The sponsor provided a copy of the French label and the English translation. However, there is a warning the Canadian label in both

French and English. The sponsor explains that they were required to insert this warning because the Hoechst version of articaine had been previously required to have the warning. They note that they have never received a report of methemoglobinemia.

There is no mention of methemoglobinemia in the French label. The sponsor did not answer the question as to why Hoechst had to put the warning in their label. On 3-28-00 I asked the CSO to contact the sponsor and ask them to explain if Hoechst put the methemoglobinemia warning in their label as general information about dental anesthesia or because of specific cases.

Conclusions: The sponsor appears to have satisfied issues 2, 3 4, 5, and 6 from our recent teleconferences. Issues 1, 7, and 8 are still outstanding. Therefore, under the current circumstances, I would recommend an Approvable (AE) action be taken.

/S/ DDS 3/28/00

Harold Blatt, D.D.S.
Clinical Reviewer

/S/ 3/29/00

Bob Rappaport, M.D.
Deputy Director and Medical Team Leader, Pain and Anesthetic Drugs, HFD-170
Secondary Reviewer

cc:
Orig NDA 20-971
HFD-170/DIV FILES
HFD-170/McCormick
HFD-170/Rappaport
HFD-170/Blatt
HFD-170/Governale

N20971Response to FDAQuestions.322.doc

NDA 20-971/AZ
Sponsor: Deproco Inc.
Principal Investigator: N/A
Drug Name: Septanest (articaine hydrochloride 4% with epinephrine 1:100,00 and 1:200,000)
Type of Submission: Response to Approvable Letter dated May 7, 1999
Proposed Indication: For infiltration or nerve block anesthesia for dentistry
Reviewer: Harold Blatt, D.D.S.
Team Leader: Bob Rappaport, M.D.
Letter Date by Sponsor: February 3, 2000
Date Received by CDER: February 3, 2000
Date Received by Reviewer: February 7, 2000
Date Review Completed: February 25, 2000
CSO: Deborah Fong

Background:

This review addresses the sponsor's response to our second Approvable (AE) Letter dated May 7, 1999. The response to our first Approvable Letter dated February 8, 1999 were complete however, CMC issues remained regarding product formulation and epinephrine concentrations in the products. The sponsor's responses to issues 1-4 are CMC issues and issue 7 is a DDMAC issue. Only issues 5 and 6 are clinical issues. These clinical issues including sponsor's responses and this reviewer's comments are given below:

FDA Issue No. 5
In addition, it will be necessary for you to submit revised draft labeling for the drug. The labeling should be identical in content to the enclosed labeling (text for the package insert).

Sponsor's Response to Issue No. 5:

Attachment C contains the revised draft labeling (package insert) for the Septanest products This draft labeling is similar to the draft attached to the FDA's Second Approvable Letter. The Sponsor has addressed the questions posed in the FDA's draft insert and incorporated the additional information requested.

The Agency requested that the Sponsor provide references or citations for its dosage recommendations. As explained in my letter of March 9. 1999, the dosage recommendations included in the insert are identical to the dosage recommendations used by Hoechst and the Sponsor in marketing articaine products worldwide. In the Sponsor's own clinical trials, approximately 75% of the subjects receiving articaine were administered dosages consistent with these recommendations. In addition, attached is a statement by [redacted], a leading authority on dental anesthetics, summarizing his conclusions that the recommended dosages are

consistent with the dosages administered in clinical dentistry

Reviewer's Comment: This reviewer compared the sponsor's revised draft labeling to the labeling attached to the second Approvable Letter and found the following discrepancies:

-
- DRAFT
-
-

FDA Issue No. 6

Under 21 CFR 314.50 (d)(5)(vi)(b), ewe request that you update your NDA by submitting all safety information you now have regarding your new drug. Please provide updated information as listed below. The update should cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission (2) other dosage forms, and (3) other dose levels, etc.

Sponsor's Response to Issue No.6:

All studies conducted by the sponsor were completed by the time the Sponsor filed NDA 20-971 and the study reports from those studies were included with the application. The sponsor has not conducted any clinical trials since the submission of NDA 20-971.

Reviewer's Comment: This response is acceptable.

FDA Issue No. 6.1

Retabulation of all safety data including results of trials that were still ongoing at the time of NDA submission. The tabulation can take the same form as in your initial submission. Tables comparing adverse reactions at the time of the NDA was submitted

versus now will certainly facilitate review.

Sponsor's Response to Issue No.6.1:

Because the Sponsor has not conducted any additional trials since submission of NDA 20-971, the tables contained in the application remain accurate and complete.

Reviewer's Comment: This response is acceptable.

FDA Issue No. 6.2
Retabulation of drop outs with new dropouts identified. Discuss, if appropriate.
Sponsor's Response to Issue No.6.2:

Because the Sponsor has not conducted any additional trials since submission of NDA 20-971, there have been no new dropouts.

Reviewer's Comment: This response is acceptable.

FDA Issue No. 6.3
Details of any significant changes or findings.

Sponsor's Response to Issue No.6.3:

Because the Sponsor has not conducted any additional trials since submission of NDA 20-971, there are no new changes to report.

Reviewer's Comment: This response is acceptable.

FDA Issue No. 6.4
Summary of worldwide experience on the4 safety of this drug.

Sponsor's Response to Issue 6.4:

Attachment E contains a summary of the worldwide marketing experience and adverse event reports for Septanest products. It is important to note that the formulations of the Septanest products proposed for sale in the U.S. and currently sold in Great Britain are slightly different than the formulations used in the products sold worldwide. The products sold outside the U.S. and Great Britain contain the additional preservative ingredient EDTA.

Since the Sponsor's submission of its Response Letter (Amendment No. 2 to NDA 20-971) on March 9, 1999, the Sponsor has become aware of sixteen (16) additional adverse event reports us follows:

France:
Septanest 1:100,000 - 3 adverse events

Belgium:

Septanest 1: 100,000 - 2 adverse events
Septanest 1:200,000- 1 adverse event

Attachment F contains copies of the adverse event reports from France, The first set of reports included in the attachment are entirely in French, while the second set of reports includes English translations of relevant information.

The Sponsor has not received copies of the adverse events reported from Belgium. However. the events were described to the Sponsor as follows:

Septanest 1:100,000:

one patient experienced "heart beating, vomiting, pallor, and , sweating"
another patient experienced a "fainting sensation"

Septanest 1:200,000:

- the dentist reporting the adverse event noted that the product "makes, the patients feel sleepy"

Reviewer's Comment: This reviewer looked at the Belgian reports given above and English translations of the French reports. The adverse events appear to be the result of accidental intravascular injections, allergic responses, and infection and are already listed in the label. Most of these adverse events resolved within hours and the longest incident resolved completely in 15 days. This sponsor's response is acceptable.

FDA Issue 6.5

Case report forms for each patient who died during a clinical study or who did not complete a study because of an adverse event.

Sponsor's Response to Issue 6.5:

As noted in the NDA, no patients died during the Sponsor's clinical trials. One subject receiving lidocaine withdrew from a study (Study No. S96001.02US) due to an adverse event. The case report form for this subject was included with the NDA (Volume 1.63, pages 1-12).

Reviewer's Comment: This reviewer looked at the CRF. The patient developed mild chest tightness and moderate dizziness that resolved. This may have been due to accidental intravascular injection or to anxiety. Sponsor's response is acceptable.

FDA Issue 6.6

English translations of any approved foreign labeling not previously submitted.

Sponsor's Response to Issue 6.6:

The Sponsor has already submitted English translations of all package inserts used

outside the U.S.

Reviewer's Comment: This response is acceptable.

FDA Issue 6.7
Information suggesting a substantial difference in the rate of occurrence of common but less serious adverse events.

Sponsor's Response to Issue 6.7:

The Sponsor is not aware of any information that suggests a substantial difference in the rate of occurrence of common, but less serious, adverse events.

Reviewer's Comment: This response is acceptable.

Conclusions:

The sponsor's overall response appears to be complete and acceptable for the clinical issues raised in the Approvable Letter of May 7, 1999 with one exception. The sponsor should replace " ——— " with the original term " ——— " in the ADVERSE REACTIONS section under *Nervous System* and add " ——— " under *Nervous System* in its correct alphabetical position.

/S/ DDS 2-25-00
Harold Blatt, D.D.S.
Clinical Reviewer

/S/ 2/25/00
Bob Rappaport, M.D.
Deputy Director and Team Leader, HFD-170
Secondary Reviewer

cc:
Orig NDA 20-971/AZ
HFD-170/DIV FILES
HFD-170/Rappaport
HFD-170/Blatt
HFD-170/~~Chamberlin~~ Gavernale

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NDA 20-971 (BL)
Sponsor: Deproco Inc. 524-C Quigley Blvd., New Castle, DE 19720
Name: Septanest® 1:200,000 and Septanest® 1:100,000 (4% articaine plus 1/200,000 epinephrine and 4% articaine plus 1/100,000 epinephrine)
Type of Submission: Background package for pending meeting request.
Proposed Indication:
Reviewer: Harold Blatt, D.D.S.
Team Leader: Bob Rappaport, M.D.
Letter Date by Sponsor: March 9, 1999
Date Received by CDER: March 9, 1999
Date Received by Reviewer: March 22, 1999
Date Review Completed: April 27, 1999
CSO: Susmita Samanta

Background: On January 29, 1999 the FDA issued and Approvable Letter stating that the Application could be approved if the sponsor completely and adequately addressed the issues raised by the Agency.

Indications: For infiltration and nerve block anesthesia in clinical dentistry.

Objectives: The sponsor has provided their response to each issue raised by the Agency in our January 29, 1999 Approvable Letter as follows:

FDA Issue No.1

Recently, our inspectors could not complete inspection of your ' manufacturing facilities for conformance with current good manufacturing practices (cGMP) because the facilities were not ready for inspection. A satisfactory inspection will be required before this application may be approved.

Sponsor's Response to Issue No.1:

In their submission the sponsor enclosed a copy of an e-mail message from Richard Friedman (CDER, Office of Compliance, Division of Manufacturing and Product Quality, Foreign Inspection Team) to . ' stating that the Agency has classified ' : facility as "an acceptable supplier of) produced by " They understood, from a conversation with Mr. Ken Nolan, that this classification obviates the need for a pre-approval inspection.

FDA Issue No.2:

Labeling on the cartridge must be imprinted with the following phrase "Contains sodium metabisulfite

Sponsor's Response to Issue No.2:

The labeling on the cartridge has been revised to include the phrase "Contains sodium metabisulfite"

FDA Issue No.3:

Assurance must be provided that the imprinting on the cartridge does not rub off with normal use.

Sponsor's Response to Issue No.3:

The sponsor stated that the cartridges will be [redacted], that is, the cartridge manufacturer will use [redacted] The printing is consequently [redacted] and cannot rub off. The printing will be gold or silver according to the strength.

FDA Issue No.4:

The names "Septanest [redacted] are misleading by not revealing both ingredients, articaine and epinephrine. The brand names for these products will need to be revised accordingly. We suggest that the drug product's brand name be followed by the strength for both ingredients.

Sponsor's Response to Issue No.4:

As noted in the revised labeling attached to this letter, the Sponsor proposes the following names for the products:

Septanest® [redacted] (articaine hydrochloride 4% with epinephrine 1:100,000 Injection) [redacted]

These names are consistent with the product names used by the Sponsor worldwide. Moreover, as explained in detail in the Sponsor's Response to Issue No.7, the designation of the epinephrine concentrations conforms to the "state-of-the-art" for epinephrine containing products.

If the Agency is unwilling to accept the designation of the epinephrine concentrations above, the Sponsor would request a teleconference or meeting with the Agency to discuss the issue further.

FDA Issue No.5;

Include a limit for each specified impurity originating from articaine HCl and epinephrine tartrate and a limit for total impurities in the regulatory specifications for the drug product.

Sponsor's Response to Issue No.5:

The only degradation product originating from articaine HCl is 4-methyl-3-[2-(propylamino) propionamido]-2 thiophene carboxylic acid, or articainic acid, as mentioned in NDA 20-971under paragraph 2.1.1.4.1 of the Chemistry, Manufacturing, and Control Section (Volume 1.5, page 15). The limit for this degradation product is: [redacted] % of articainic acid.

The main degradation product formed by the epinephrine oxidation is adrenochrome as mentioned in NDA 20-971 under paragraph 2.2.1.4.1 of the Chemistry, Manufacturing, and Control Section (Volume 1.5, page 99). The limits are:

- Percentage for adrenochrome [redacted]
- Percentage of total impurities: [redacted]

The sponsor also provided the revised regulatory specifications of the drug products, including these new limits which are valid from release to the end of the shelf life.

FDA Issue No.6:

Update carton [and can] labeling to reflect new brand names. Indication on carton [and can] labeling should refer to package insert or read exactly as the package insert.

Sponsor's Response to Issue No.6:

The sponsor provided the carton and can labeling for the Septanest® products. The labeling is consistent with the proposed package insert and includes the product names described in the Sponsor's Response to Issue No.4 above.

FDA Issue No. 7:

Overage for any product to merely extend the expiration dating is not allowed. Please label the product to reflect the epinephrine content. The recommended expiration dating period for the drug product is — months.

Sponsor's Response to Issue No.7:

With regard to the concentration of epinephrine and the labeling:

- The Sponsor requests approval for a concentration up to 15% over the labeled quantity of epinephrine with an expiration dating period of — months;
- However, if requested by the Agency, the Sponsor would accept a — manufacturing overage of epinephrine with an expiration dating period of — months.
- The Sponsor will not be able to market the product with a 5% epinephrine overage with an expiration dating period of — months as proposed by the Agency in its Approvable Letter. Such products simply could not be marketed with this shelf-life because the products are manufactured in France, exported to the U.S. for marketing through an importer, and then passed through other dental distributors. Given the length of time it will take to deliver the drug products from the manufacturer in France to the dental practitioners in the U.S., a — month shelf life is not adequate for marketing.
-
- Justification of the Overage:

The Sponsor incorporated by reference its submission of February 8, 1999, providing support for the safe use of a 15% overage of epinephrine.

Further, at the outset, the Sponsor pointed out that epinephrine is commercially available in a variety of strengths, formulations and packaging systems. The Sponsor believed the history of epinephrine usage in other products should be considered in the overage evaluation of safety and in the development of standards.

The sponsor noted that several dental anesthetics containing epinephrine at levels analogous to those of

Septanest® have long histories of usage, first under NDA's and later as generic products. USP monographs for these products also allow the 90% to 115.0% range for epinephrine content without limiting degradation products (sponsor provided copies of USP monographs with this submission). This upper acceptance limit of 115.0 % suggests that an overage of 10 to 15% is permitted for these epinephrine-containing products.

The sponsor stated that the manufacturing loss for Septanest® products is approximately . —— '% for epinephrine.

The Sponsor is further aware that it is the common and usual industry practice -- and the state-of-the-art -- for dental anesthetic manufacturers to add a 10-15% overage of epinephrine to those dental anesthetics containing epinephrine.

To demonstrate this, the Sponsor conducted a set of experiments to determine the amount of epinephrine in local injectable anesthetic products manufactured by other companies. These competing products were obtained through commercial sources and are currently used in clinical dentistry. The measured content of epinephrine was compared to the labeled amount of this ingredient.

According to the sponsor, the data obtained demonstrated that the amount of epinephrine in Septanest® products at release is comparable to the amount in competing products after a storage period from ——— months. This table below showed that at the time of product release, the overage in the competitive products is about 10 to 15%:

Novocol 13%
Hoechst 15%
Septodont 10%

It is usual practice for products containing epinephrine to use an overage to maintain an acceptable shelf-life. For example, as noted in Table 2, the initial epinephrine content of Hoechst's Ultracaine DS Forte (articaine hydrochloride 4% with epinephrine 1/100,000) is 114% of the labeled quantity, while at the end of the shelf-life the content is 103% of the labeled quantity. Therefore, epinephrine overages usually are used not only to compensate for manufacturing loss, but also to maintain an acceptable shelf-life.

According to the documentation available from the USP, the USP standard was adopted in 1953. At that time, the USP surveyed certain products on the market and discovered that they ranged in epinephrine concentration from 90% to 115%. The USP clearly intended, therefore, that solutions of epinephrine - even if labeled with values such as 1:1000 (as was the 1953 product), or 1:100,000 or 1:200,000 could contain up to 115% of the labeled value of the epinephrine.

The 90%-115% standard range for epinephrine established in 1953 was adopted for many other epinephrine-containing anesthetics - including Lidocaine and Epinephrine Injection and Prilocaine and Epinephrine Injection, apparently without change or comment by the USP. The dental industry has used this standard range since at least 1953 and has consistently labeled its dental anesthetic products with, for instance 1:50,000, 1:100,000 and 1:200,000 epinephrine concentrations even if they contain an overage of up to 115%. The expiration dates for such products are likewise based upon meeting the 90-115% range and, thus, the universal practice followed by the dental anesthetic manufacturing industry is to establish an expiration date based upon when the 1:50,000, or the 1:100,000, or the 1:200,000 product falls below the 90% of labeled value amount of epinephrine.

Therefore, the Sponsor proposes to comply with the USP position; that is, 90 to 115% of 1 mg/l 00 mL for Septanest® — and 90 to 115% of 0.5 mg/100 mL for Septanest® and to label the products as described in the response to issue 4 above.

FDA Issue No.8:

In addition, it will be necessary for you to submit final printed labeling (FPL) for the drug. The labeling should be identical in content to the enclosed labeling (text for the package insert, immediate container and carton labels).

Please submit 20 copies of the final printed labeling ten of which are individually mounted on heavy weight paper or similar material.

Sponsor's Response to Issue No.8:

The Sponsor has modified the draft insert included with the Approvable Letter in preparing its revised package insert. The Sponsor has addressed the questions posed in the FDA's draft insert and incorporated the additional information requested, as well as making a number of minor changes to the text proposed by the Agency.

The Agency requested that the Sponsor provide references or citations for its dosage recommendations. The dosage recommendations included in the insert are identical to the dosage recommendations used by Hoechst and the Sponsor in marketing articaine products worldwide. In the Sponsor's own clinical trials, approximately 75% of the subjects receiving articaine were administered dosages consistent with these recommendations. The sponsor also noted that [redacted], a leading authority on dental anesthetics, reviewed the dosage recommendations and concluded that they are consistent with dental practices.

As noted in the Sponsor's Response to Issue No.6, the sponsor also attached copies of the revised draft labels for the cans and cartons. The Sponsor will submit final printed labeling (package insert, carton label, can label, and cartridge label) as soon as the Agency indicates that these drafts are acceptable.

FDA Issue No.9:

Under 21 CFR 314.50(d)(5)(vi)(b), we request that you update your NDA hi' submitting all safety information you now have regarding your new drug Please pro vide updated information as listed below. The update should cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels, etc.

Sponsor's Response to Issue No.9:

All studies conducted by the Sponsor were completed by the time the Sponsor filed NDA 20-971 and the study reports from those studies were included with the application. The Sponsor has not conducted any clinical trials since the submission of NDA 20-971.

Issue 9 1. *Retabulation of all safety data including results of trials that were still ongoing at the time of NDA submission. The tabulation can take the same form as in your initial submission. Tables comparing adverse reactions at the time the NDA was submitted versus now' will certainly facilitate review*

Sponsor's Response to Issue 9.1:

Because the Sponsor has not conducted any additional trials since submission of NDA 20-971 the tables contained in the application remain accurate and complete.

Issue 9.2. *Retabulation of drop-outs with new drop-outs identified. Discuss, if appropriate.*

Sponsor's Response to Issue 9.2:

Because the Sponsor has not conducted any additional trials since submission of NDA 20-971 there have been no new drop-outs.

Issue 9.3. *Details of any significant changes or findings.* Sponsor's Response to Issue 9.3:

Because the Sponsor has not conducted any additional trials since submission of NDA 20-971, there are no new changes or findings to report.

Issue 9 4 *Summary of worldwide experience on the safety of this drug.* Sponsor's Response to Issue 9.4.

The sponsor provided a summary of the worldwide marketing experience and adverse event reports for Septanest® products. It is important to note that the formulations for the Septanest® products proposed for sale in the U.S. and currently sold in Great Britain are slightly different than the formulations used in the products sold worldwide. The products sold outside the U.S. and Great Britain contain the additional preservative ingredient FDTA.

Since the Sponsor's submission of its Four Month Safety Update on August 6, 1998, the Sponsor has become aware of one additional adverse event report in France. The sponsor provided the adverse event report, with relevant information translated into English.

This reviewer has requested the project manager to contact the sponsor to find out if any follow-up information is available on this AE. We are awaiting the sponsor's response.

Issue 9.5 *Case report forms for each patient who died during a clinical study or who did not complete a study because of an adverse event.*

Sponsor's Response to Issue 9.5:

As noted in the NDA, no patients died during the Sponsor's clinical trials. One subject receiving lidocaine withdrew from a study (Study No. S96001 .02U5) due to an adverse event. The case report form for this subject was included with the NDA (Volume 1.63, pages 1-12).

Issue 9 6 *English translations of any approved foreign labeling not previously submitted*

Sponsor's Response to Issue 9.6:

The sponsor provided the package inserts used in Great Britain.

Issue 9.7. *Information suggesting a substantial difference in the rate of occurrence of common, but less serious, adverse events.*

Sponsor's Response to Issue 9.7;

The Sponsor is not aware of any information that suggests a substantial difference in the rate of occurrence of common, but less serious, adverse events.

FDA Issue No. 10:

In addition, p/ease submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock- up form, not final print. Please send one copy to the Division of Anesthetic, Critical Care, and Addiction Drug Products, HFD-170 and two copies of both the promotional materials and the package insert directly to Division of Drug Marketing, Advertising, and Communications.

Sponsor's Response to Issue No.10:

The sponsor provided a draft copy of the introductory promotional materials they intend to use.

Further, as requested, the Sponsor will submit two copies of the promotional materials and package insert to the Division of Drug Marketing, Advertising, and Communications.

Comments:

1. Issue 9.4 Since the Sponsor's submission of its Four-Month Safety Update on August 6, 1998, the Sponsor has become aware of one additional adverse event report in France. The sponsor provided the adverse event report, with relevant information translated into English.

This reviewer has requested the project manager contact the sponsor to find out if there is any follow-up information is available on this AE. [Please see Attachment "H" of the submission.] The AE appears to have occurred post-marketing and not during one of the clinical trials. We may wish to add a line in the labeling depending on what we find out. The sponsor's first response to our request was still incomplete and we are awaiting further information.

2. The sponsor has submitted a proposed revised draft labeling in this submission in response to our AE letter.

A) In the PHARMACODYNAMICS SECTION :

DRAFT

After consultation with the Biopharm Team Leader, we would suggest the following alternative wording,

DRAFT

"[From Lipp, et al., "Exogenous and Endogenous Plasma Levels of Epinephrine During Dental treatment Under Local Anesthetic" Regional Anesthesia 1993: 18: 6-12]. We also recommend the sponsor delete the last two sentences of the this proposed draft paragraph beginning with,

DRAFT

The original statement mentioned in section A) above comes from Vol. 1.22 of the original submission. I have consulted with the Biopharm Team Leader and provided her with the references in Vol. 1.40, and Vol. 1.22 of the original NDA submission regarding this issue. The Biopharm Team Leader and I reviewed the 5 articles related to this issue. While these studies were largely carried out in healthy young volunteers with no apparent serious consequences, some of the investigators voiced concern about cardio-hemodynamic changes in older patients with cardiovascular disease. This reviewer would echo that concern and suggest appropriate wording be placed in the labeling. As currently stated the language appears to be somewhat misleading. Also we are still not clear as to whether the increased levels of plasma epinephrine occurred as a result of intravascular injection, increased tissue manipulation and bleeding during the procedure, or some other reason. We are, however, reasonably certain it is not due to endogenous epinephrine levels brought on by the stress of the procedure.

3.In the ADVERSE EVENTS SECTION after Table 1 they deleted the phrase,

from the sentence which begins,

"

We would like to know why this phrase was deleted.

Conclusions: The sponsor appears to have satisfied issues1, 2, 5, and 10 from our AE letter of January 29, 1999. Issues 3, 4, 6, 7, 8, and 9 are still outstanding. These remaining outstanding issues will be reviewed by ONDC. From a clinical perspective, the items mentioned in the Comments section above regarding labeling changes and clarifications will also have to be resolved. Therefore, under the current circumstances, I would recommend an Approvable (AE) action be taken.

/S/ DDS 4-27-99

Harold Blatt, D.D.S.
Clinical Reviewer

/S/

Bob Rappaport, M.D.
Deputy Director and Medical Team Leader, Pain and Anesthetic Drugs, HFD-170
Secondary Reviewer

cc:

Orig NDA 20-971 (BL)
HFD-170/DIV FILES
HFD-170/McCormick
HFD-170/Rappaport
HFD-170/Blatt
HFD-170/~~Chamberlin~~ Samanta

N20971Blresp.doc

DIVISION OF ANESTHETIC, CRITICAL CARE AND ADDICTION DRUG PRODUCTS

Brand Name:	Septanest [redacted]
Generic Name:	articaine hydrochloride 4% with epinephrine 1:200,000 and articaine hydrochloride 4% with epinephrine 1:100,000
Indication:	For infiltration or nerve block Anesthesia for dentistry
NDA Classification:	1S
NDA Number:	20-971
Original Receipt Date:	March 30, 1998
Clinical Reviewer:	Harold J. Blatt, D.D.S.
Review Completed:	October 2, 1998

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for most routine procedures. The actual volumes and concentrations to be used depend on a number of factors such as type and extent of surgical procedure, depth of anesthesia and degree of muscular relaxation and condition of the patient. In all cases the lowest concentration and smallest dose that will produce the desired result should be given. Dosages should be reduced for pediatric patients and for the elderly and debilitated patients and patients with cardiac and/or liver disease.

The onset of anesthesia and the duration of anesthesia are proportional to the volume and concentration (i.e., total dose) of local anesthetic used. Although the incidence of side effects with Septanest® [redacted] is quite low, caution should be exercised when employing large volumes or concentrations, since the incidence of side effects is directly proportional to the total dose of local anesthetic agent injected.

MAXIMUM RECOMMENDED DOSAGES

DRAFT

[from "Annotated Labeling", Vol. 1.3, p.10]

SECTION 2.5 FOREIGN MARKETING

Septanest® was registered in 13 European countries and Canada between 1988 and 1997. [redacted] for both the 1/100,000 and 1/200,000 formulations, and in [redacted] for the 1/100,000 formulation. Septanest has never been withdrawn from the market in any country.

[from Vol. 1.3, p. 15]

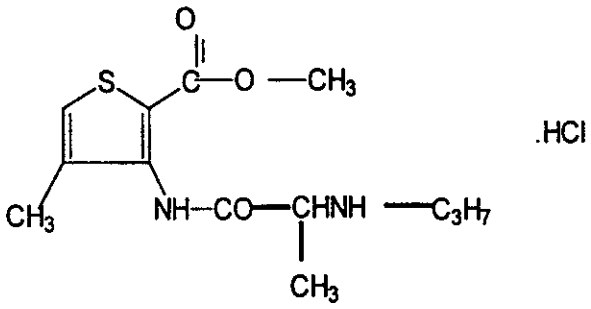
SECTION 3.0 CHEMISTRY

Compound Name: articaine HCl

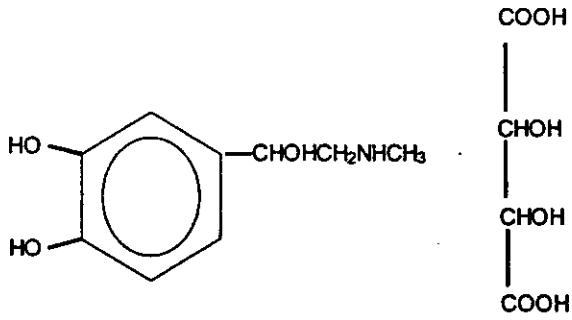
Chemical Name: 4-Methyl-3-[2-(propylamino)-propionamido]-2-thiophene-carboxylic acid, methyl ester hydrochloride.

Molecular Weight: 320.84

The structural formula is:



Epinephrine, (-)-1-(3,4-Dihydroxyphenyl)-2-methylamino-ethanol (+) tartrate (1:1 salt), is a vasoconstrictor that is added to articaine HCl in concentrations of either 1/100,000 or 1/200,000. It has a molecular weight of 333.3. The structural formula for epinephrine is displayed below:



Septanest® Injection is a sterile solution for use in dental anesthesia. It contains two active ingredients, articaine hydrochloride and epinephrine bitartrate.

Articaine hydrochloride is a local anesthetic of the amide type. Epinephrine bitartrate is used as a vasoconstrictor to prolong effectiveness and reduce eventual bleeding.

Inactive ingredients in the formulation are sodium chloride, sodium metabisulfite, and sodium hydroxide. Sodium metabisulfite is a stabilizer used to improve the stability of epinephrine which has a known susceptibility to oxidation. Septanest® is packaged in a single-use container, consisting of a cartridge for use in a standard dental syringe. Each cartridge contains 1.7 mm, of solution.

[Item 4., Vol. 1.3, pp.16-17]

SECTION 4.0 ANIMAL PHARMACOLOGY/TOXICOLOGY

The sponsor has summarized the pharm/tox data for Septanest in Section 5.1 of Item 5, Vol. 1.3 of the NDA. The following is a condensation of that summary.

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 toxokinetic 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]

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SECTION 5.0 DESCRIPTION OF CLINICAL DATA SOURCES

SECTION 5.1 STUDY TYPE AND DESIGN/PATIENT ENUMERATION

SUMMARY OF ALL STUDIES SUBMITTED TO THIS NDA			
Studies	**Type**	**Enumeration by Treatment Group**	
		Septanest	Placebo/Active Control
Pharmacodynamic and Pharmacokinetic Studies (12)	Various designs including open-non-randomized, randomized cross-over, parallel group, double-blind cross-over, and randomized double-blind cross-over.	A total of 209 patients were studied	
Primary Clinical Trials	Single-dose, randomized, double-blind, parallel-group, active controlled , multi-center for efficacy and safety	882	443
Supportive Clinical Trials (2)	Randomized, single-blind, parallel group, active-controlled, single center for efficacy and safety	101	99

SECTION 5.2 DEMOGRAPHICS

See sections 7.2.1.4, 7.2.2.4, and 7.2.3.4 of this review.

SECTION 5.3 EXTENT OF EXPOSURE

See section 8.3.1 of this review.

SECTION 6.0 SUMMARY OF HUMAN PHARMACOKINETICS

The results of the sponsor's study (S97001) to evaluate the pharmacokinetics of articaine with epinephrine was compared to published results obtained with other formulations of articaine with epinephrine (including a report of articaine pharmacokinetics in pediatric patients). In study S97001, the pharmacokinetics of articaine were determined in 20 healthy subjects (10 male, 10 female) following single and multiple doses of Septanest — 4% articaine HCl with 1:200,000 epinephrine) administered by maxillary infiltration with the formulation proposed for marketing.

The comparison of S97001 to the published studies indicate that articaine is rapidly metabolized to articainic acid following administration of Septanest with 1:200,000 epinephrine and other formulations of articaine with epinephrine. Peak plasma concentrations of articaine are related to dose and generally occur within 0.5 hour after administration. Plasma concentrations are comparable in pediatric patients and adults. The short half-life of articaine parallels its anesthetic effects.

No bioavailability or bioequivalence studies were performed by Deproco, Inc. for any Septanest formulation of articaine HCl and no such studies are known to have been published using other commercial formulations.

SECTION 7.0 EFFICACY FINDINGS

SECTION 7.1 OVERVIEW OF CLINICAL STUDIES

Clinical data for support of the request for market approval of Septanest® in the United States in nerve block and infiltration anesthesia for routine dental procedures includes both historical experience with articaine/epinephrine formulations marketed in Europe (since 1978) and Canada and Deproco, Inc.-sponsored clinical studies. The clinical trials were conducted under IND and were designed in agreement with the FDA. The studies were designed determine the pharmacokinetics of single and multiple doses of 4% articaine HCl (Septanest® (2) to compare the safety of Septanest® to that of a standard, approved local dental anesthetic, 2% lidocaine HCl with 1:100,000 epinephrine, and (3) to confirm the effectiveness of Septanest® The studies that were planned and conducted by Deproco, Inc. were as follows:

1. A pharmacokinetic study following single and multiple dosing with Septanest® in 20 healthy volunteers protocol S97001) to investigate the metabolism and excretion of articaine and its metabolites, articainic acid and articainic acid glucuronide.

2. Two (2) Phase III double-blind, randomized, active-controlled clinical trials to compare the safety of Septanest® with the standard, approved dental anesthetic 2% lidocaine hydrochloride with 1:100,000 epinephrine and secondarily, to determine the effectiveness of Septanest® in approximately 1500 total patients, 4 to 80 years of age, in the United States and the United Kingdom. In order to enroll an adequate number of patients, especially children between 4 and 13 years of age, three studies using essentially identical protocols were conducted (protocols S96001.02, S96002.01, and S96001.O2UK).

3. A Phase II study with 20 healthy volunteers, measuring efficacy in terms of the pharmacodynamic parameters of onset of anesthesia, depth of anesthesia and duration of anesthesia using an electric pulp tester (protocol S97001)

Since articaine was first introduced by Hoechst in 1976 (as Ultracain®), the efficacy and safety of articaine/epinephrine formulations marketed by Specialites Septodont, Hoechst and other manufacturers as local dental anesthetics have become well known and their use in standard dental procedures is extensive in Europe and Canada. A number of studies utilizing the Hoechst formulations of articaine have been published. In addition, at the time of submission of the IND (October 18, 1996) for the above mentioned trials, cartridges of the Septanest® European formulations of articaine/epinephrine had been marketed. Due to the published pharmacodynamics and clinical efficacy and safety of articaine/epinephrine combinations available at the time of the IND submission a Phase II study (n=20) to provide pharmacodynamic and pharmacokinetic data on Septanest was agreed upon with the FDA. For this study (Protocol S97001), the lower epinephrine concentration (1:200,000) was chosen, since the literature indicates that this articaine/epinephrine combination would be likely to have the shortest duration of anesthesia and provide the highest blood levels of articaine and its metabolites for pharmacokinetic analysis.

The Phase III clinical trials were carried out to establish the comparable safety of 4% articaine HCl with 1:100,000 epinephrine to 2% lidocaine hydrochloride with 1:100,000 epinephrine. As part of this investigation, particular regard was to

be paid to reports of paresthesia. FDA concerns over paresthesia were raised due to recent labeling changes to lidocaine and to increases in the reporting of paresthesia to the Professional Liability Program of the Royal College of Dental Surgeons of Ontario, Canada since the introduction of articaine in that country. Consequently it was decided that, in addition to collecting adverse events, information on paresthesia would be specifically collected in two follow-up telephone interviews. The specific questions to be asked and the timing of these telephone contacts (24 hours and 7 days post procedure) were agreed upon with the FDA as referenced in the Agreement Section in this NDA.

A dose of 4% articaine hydrochloride with 1:100,000 epinephrine was chosen for the Phase III 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. To assure consistency in performance of procedures, the number of sites was to be kept as low as possible.

Simulating routine dental practice was an important factor in designing the clinical trials. Therefore, most routine dental procedures were allowed. All procedures were stratified into simple (single extractions with no complications, routine operative procedures, single apical resections and single crown procedures) or complex (multiple extractions, multiple crowns and/or bridge procedures, multiple apical resections, alveolectomies, mucogingival operations and other surgical procedures on the bone) in order to control for factors related to the procedure rather than the anesthetic. Also, in an effort to simulate clinical practice further, the actual volume of anesthetic administered was not limited by the protocol, but was administered on an "as needed" basis to achieve adequate anesthesia, not to exceed the maximum recommended dosage of 7 mg/kg.

Since anesthetic is routinely administered to young children, pediatric use of articaine in children as young as 4 years of age was to be investigated in the clinical trials.

[Item 8.2, Vol. 1.22, pp. 7-9]

SECTION 7.2 SUMMARY OF STUDIES PERTINENT TO EFFICACY

SECTION 7.2.1 STUDY 96001.02 UK

Section 7.2.1.1 Protocol Synopsis

Title: A Single Dose Study to Evaluate the Safety and Efficacy of Septanest — (4% articaine HCl) with 1:100.000 Epinephrine Versus 2% Lidocaine HCl with 1:100,000 Epinephrine in the Treatment of General Dental Procedures

Objective: "This single-dose , double blind, randomized, parallel group, multicenter, Phase III study is designed to demonstrate that 4% articaine HCl with 1:100,000 epinephrine is as safe as 2% lidocaine HCl with 1:100,000 epinephrine, both administered parenterally, when use in clinical dentistry. This study is also designed to show that 4% articaine with 1:100,000 epinephrine is efficacious.

[Item 2.0, Vol. 1.22, p.238]

Study Design:

"This single-dose, double-blind, randomized, parallel -group, active-controlled, multicenter study will compare the safety and efficacy of 4% articaine HCl with 1:100,000 epinephrine versus 2% lidocaine HCl with 1:100,000 epinephrine administered parenterally. Eight UK sites will enroll approximately 68 patients to provide a total of 500 completed patients (544 total patients). At each site, patients will be randomly be assigned in a 2:1 ratio, such that 334 completed patients (364 total patients) will receive articaine and 166 completed patients (182 total patients) will receive lidocaine.

Inclusion Criteria

Patients were to meet the following criteria to be eligible for participation in the study:

- Required infiltration anesthesia or nerve block anesthesia for any of the following: single extraction with no complications; multiple extractions; apical resections; alveolectomies; routine operative and crown and bridge procedures on vital teeth; and other routine procedures requiring oral local anesthesia In addition, patients who needed mucogingival operations and other surgical procedures on the bone when long-lasting ischemia and analgesia were required, were also eligible;
- Were between 4 and 80 years of age, inclusive;
- Must have had clinical laboratory values within normal range as determined by the reference laboratory;

Exclusion Criteria

Patients were to be excluded if they met any of the following:

- Had bony, fully impacted teeth or maxillo-facial surgery;
- Had any known or suspected allergies or sensitivities to sulfites or amide-type local anesthetics or any of the ingredients in the test solutions;
- Had concomitant cardiac or neurologic disease;
- Had a history of severe shock, paroxysmal tachycardia, frequent arrhythmia, severe untreated hypertension, or bronchial asthma;
- Were considered an inappropriate candidate for the study due to a concomitant medical or psychiatric condition;
- Had evidence of soft tissue infection near the proposed injection site; but localized periapical or periodontal infections were permitted;
- Were taking monoamine oxidase (MAO) inhibitors, tricyclic antidepressants, phenothiazine, butyrophenones, vasopressor drugs, or ergot-type oxytocic drugs;
- Received chloroform, halothane, cyclopropane, trichloroethylene, or related anesthetics during the treatment visit;
- Were expected to require nitrous oxide or any general anesthesia;
- Had taken aspirin, acetaminophen, nonsteroidal anti inflammatory drugs (NSAIDs), or other analgesic agents within 24 hours prior to administration of study medication;
- Had previously participated in this study or had taken an investigational drug(s) or participated in another study within four weeks prior to initiation of treatment.

The trial will consist of a screening visit, a treatment visit, and 2 follow-up telephone calls. At the screening visit, patients who meet all eligibility criteria and sign an informed consent form will provide a medical history and will have a brief physical examination, screening laboratory assessment and screening vital signs. Patients who meet all entry criteria will return for the treatment visit within the next eight days. At this time the patient will be randomized to one of two treatment groups . Baseline vital signs will be measured and study drug will then be administered. At one and five minutes following administration of the study drug, vital signs will again be obtained. Subsequently, the dental procedure will be performed followed by another measurement of vital signs and a brief physical examination. The patient will be asked to mark the level of pain experienced on a 10 cm Visual Analog Scale (VAS) with 0= no pain and 10=worst pain imaginable. A similar VAS will be used for the investigator evaluation. For children 4 through 12 years of age, a 10 cm VAS with "smiley faces" will be used. Any adverse events that occur during the treatment visit will be recorded by the investigator. The patient will then be discharged. Within 24 hours, a representative from the investigative site will telephone the patient to obtain a follow-up

report of any adverse events that may have occurred after the patient was discharged. A second telephone call will be made 7 days after treatment to again obtain a follow-up report of any adverse events that may have occurred or persisted since the last follow-up call. All patients who receive study medication will be included in the safety evaluations of adverse events and vital signs. All patients randomized will be evaluated for efficacy."

[Item 3.0, Vol. 1.22, p. 239]

"Although eight cartridges of study drug will be provided for each patient, the dose of study medication required for most procedures usually consists of one to three cartridges for adults and one cartridge for children. In more difficult cases, patients may require additional anesthesia. The additional anesthesia may be administered: however, dosages are not to exceed 7 mg/kg (3.2 mg/lb) of body weight. If a patient requires anesthesia in amounts greater than this he/she should be dropped from the study."

[Item 4.5, Vol. 1.22, p.243]

Figure 1 Study Schemata

DAYS: 1	2	3	4	5	6	7	8	9	10	11	12	13
VISIT: **Screening (Day 1)**							**Treatment (Day 8)** Randomization Study Drug Admin. Dental Procedure VAS Pain Measurement AE Assessment	**Follow-up #1 (Day 9)** Telephone Call AE Assessment			**Follow-up #2 (Day 13)** Telephone AE Assessment	

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STUDY SCHEMATIC				
Procedure	**Screening Visit[a]**	**Treatment Visit**	**Follow-up #1 Telephone Call[b]**	**Follow-up #2 Telephone Call[c]**
Informed Consent Signed	X			
Complete Medical History	X			
Physical Examination	X	X[d]		
Clinical Laboratory Evaluation[e]	X			
Vital Signs	X	X[f]		
Recent/Concomitant Medications	X[g]	X	X	X
Randomization		X		
Study Drug Administration		X		
Drug Accountability		X		
Dental Procedure		X		
VAS Measurement of Pain[h]		X		
Adverse Event Assessment		X	X	X
Assessment of Persistent Numbness/Tingling of Mouth or Face			X	X

a Within eight days prior to the treatment visit.
b Within 24 hours following discharge from the site.
c Seven days following discharge from the site.
d Prior to study drug administration and following dental procedure.
e Includes a serum pregnancy test.
f Prior to administration of study drug, 1 and 5 minutes following study drug administration, and immediately following the dental procedure.
g All medications taken within 14 days prior to screening visit.
h To be completed by the patient and investigator independently.

[Vol. 1.22, p.81]

Section 7.2.1.2 Statistical Analysis:

In this pivotal trial, which is an equivalency trial, the sponsor will try to show that there is no difference between their drug and the active control. The primary efficacy variable is the level of pain experienced during the dental procedure as measured on a VAS by both patient and investigator.

"A summary of patient characteristics, including age, race, sex, and weight, will be presented by treatment group for all patients who received study drug. Patients will be categorized by age into two groups of 1) 4 to less than 13 years old and 2) equal to or greater than 13 years old. Age and weight will be summarized by treatment group using descriptive statistics including mean, median, standard deviation, and range. Counts and percents of race and sex will be presented. Treatments will be compared for balance in age group, sex and race and strata using a Cochran-Mantel-Haenszel (CMH) test to adjust for center effects. Treatment comparisons of weight will be made with an analysis of variance (ANOVA) with treatment, center,

strata, treatment-by-center and treatment-by-strata, interaction effects. If the assumptions of normality are not met, appropriate normalizing transformations will be used."

"Descriptive statistics, including mean, median, standard deviation, and range, will be employed to summarize the total volume (mL) and the dose per unit of body weight (mg/kg) of study drug administered to patients by age group and strata."

[Items 9.1 and 9.2, Vol. 1.22 pp.256-257]

Section 7.2.1.3 Protocol Amendments

"Two amendments were made to this protocol, one on December 20,1996, and the second on January 20, 1997. Both were made prior to the enrollment of any patients in the study."

[Item 5, Vol. 1.22, p. 87]

Amendment 1:

This amendment was dated 12-20-96. It consists of a change in protocol number, the Point of Contact, and new additional wording to the Objective, Randomization, Study Drug Administration, Drug Accountability, Inclusion Criteria, Exclusion Criteria, Vital Signs, Screening Evaluation, Adverse Events, Baseline Patient Characteristics, Dose Administered, Efficacy, Case Report Forms, Appendix A, Appendix C, and Appendix E sections of the protocol.

The Objective Section adds the sentence, "This study is also designed to show that 4% articaine 1:100,000 epinephrine is efficacious."

In the Randomization section, paragraph 2, after the phrase, "...the patient will be assigned to the next available patient number in ascending order", the following phrase was added, " if the procedure is from stratum 1 and the next available patient number in descending order if the procedure(s) is from stratum 2. A minimum of 25% of the patients will be assigned to stratum 2."

Added to the Study Drug Administration section, paragraph 2, "adults over 80", who, along with children under 8 will be prohibited from the study.

In the Drug Accountability section, the phrase was rewritten to say, "...used and partially used cartridges will be destroyed at the site..."

In the Inclusion Criteria section paragraphs 1 and 2, the phrase, "...and other routine procedures requiring local anesthesia." and the sentence "Must be $\geq$ than 8 and $\leq$ 80 years of age", were added.

The following Exclusion Criteria bullets were added:

- "Bony, fully impacted teeth or maxillo-facial surgery."
- "Must not be expected to require nitrous oxide, any topical or general anesthesia."

In the Vital Signs section, the term "two minutes" was added to indicate when standing blood pressure will be taken after the change from a supine position." The last two sentences of the second paragraph were rewritten as follows: " At one minute and five minutes following initial administration of study medication, the supine blood pressure, pulse and respiration will be taken. After completion of the dental procedure, the vital signs taken prior to study medication will be repeated except for temperature."

In the Screening Evaluation section, paragraph 2, the phrase was added, "...and must not be expected to require nitrous oxide, any topical or general anesthesia."

In the Adverse Events section, paragraph 3, the second sentence was rewritten to say, " A Bio-Pharm representative (see Section 8.3) must be contacted within one working day..." Also, a FAX number was added to the address for Bio-Pharm Clinical Services.

In the Patient Baseline Characteristics section the next to last sentence was rewritten to read, "Treatment comparisons of weight will be made with an analysis of variance (ANOVA) with treatment, center, strata, treatment-by-center and treatment-by-strata interaction effects."

The Dose Administered section was changed to indicate that descriptive statistics will be used to summarize the total volume and the dose per unit of body weight by strata as well as by age group.

In the Vital Signs section, the ANOVA was reworded to include strata, and treatment-by-center interaction.

In the Efficacy section, the first sentence was reworded as follows, " Treatment comparisons of patient and investigator VAS measurements will be made with an ANOVA with treatment, center, strata, treatment-by-center interaction and treatment-by-center interaction effects."

The following was added to the Case Report Forms section,"...Case report forms must be completed within one week from the patient's second follow-up interview."

Added to Appendix A was, "11. A signed W-9 form."

Appendix C paragraph 1 was reworded to, "Effective December 5th, 1996, the FDA issued new regulations pertaining to the elements required to an informed consent. Accordingly, a signed informed consent will be obtained from all subjects participating in this study or their legally authorized representative. This consent must be dated at the time it is signed. Case records including source documentation and case report forms must note the date the informed consent was signed and this date must be prior to any participation in this study. This consent must include the following items: "

Appendix E has new wording as follows, "4.To obtain valid informed consent from each patient who participates in the study. The date must be noted in the source documentation.

Amendment 2:

"On January 20, 1997, the protocol was amended as follows following a meeting with the U.S. Food and Drug Administration and an investigators' meeting in the United Kingdom."

[Item 5, Vol. 1.22, p. 88]

This amendment was dated 1-20-97. It consists of changes to the Sign-Off List, Introduction, Study Objective, Study Drug Administration, Number of Patients to be Studied, Exclusion Criteria, Baseline Patient Characteristics, Sample Size, and Appendix B sections of the protocol.

On the Sign-Off List, Donald McGuigan D.D.S., was replaced by Suzanne Gagnon, M.D.

The Introduction section has the following new wording, "The study will be conducted in the United Kingdom (U.K.)."

The second and third sentences in the Study Objective section have been reworded as follows, "Eight U.K. will enroll approximately 68 patients to provide to provide a total of 500 completed patients (544 total patients). At each site, patients will be randomly assigned in a 2:1 ratio, such that 334 completed patients (364 total patients) will receive articaine and 166 completed patients (182 total patients) will receive lidocaine.

Also, a new sentence has been added, "For children 4 through 12 years of age, a 10 cm VAS with "smiley" faces will be used."

In the Study Drug Administration section the new sentence reads, "For purposes of this study, use in children under 4 and adults over 80 years of age is prohibited."

In the Number of Patients to be Studied section there is the following new wording, "Approximately 546 patients will be enrolled into this study to provide 500 completed patients; 334 (364) patients will receive 4% articaine HCl with 1:100,000 epinephrine and 166 (182) patients will receive 2% lidocaine HCl with 1:100,000 epinephrine. Patients from eight sites in the U.K. will be enrolled in this study. In order to meet these enrollment goals, each of the U.K. sites should attempt to enroll at least 68 patients."

Although the number in the first sentence of this section (546) is slightly different from the number (544) in the second sentence of the Study Objective section, this appears to be a typographical error. Both sentences mention 334 completed patients (364 total patients) will receive articaine and 166(182) will receive lidocaine. This amendment appears to be in response to Dr. Fred Hyman's comments in his June 28, 1996 review of this protocol in which Dr. Hyman states, "The sample size of 1500 may be larger than necessary".

The new sentence in the Exclusion Criteria section is, " Must not be expected to require nitrous oxide or any general anesthesia."

In the Baseline Patient Characteristics section the new wording is, "Patients will be categorized by age into two groups of 1) 4 to< 13 years old and 2) $\geq$ 13 years old.

The Sample Size section has the following new wording, "The sample size for this study (500 patients, 334 articaine and 166 lidocaine) is large enough to detect possible adverse events that occur at a rate of 1 in 100 in at least one articaine patient with a probability of 0.96 and at least one lidocaine patient with a probability of 0.81."

Appendix B has the new sentence, "VAS scale for children added."

Section 7.2.1.4 Conduct of Study

Patient Disposition:

"A total of 243 patients participated in this study. On hundred and fifty-nine (159) patients were randomized to receive articaine and 84 patients were randomized to receive lidocaine. One patient (#2167) in the articaine group was randomized but not treated. (This patient had taken the NSAID nabumetone within 24 hours prior to the start of the study which was one of the exclusion criteria.) Two hundred and eight patients (208, 86%) completed the study per protocol, 139 (88%) in the articaine group and 69 (82%) in the lidocaine group. A total of 34 patients did not complete the study per protocol due to protocol deviations (17, 11% articaine; 12, 14% lidocaine), being lost to follow-up (1, 1% articaine; 3, 4% lidocaine), and other reasons(1, 1% articaine, delayed follow-up visit). Because only four patients were lost to follow-up, 238 patients (98%; 157 [99%] articaine; 81 [96%] lidocaine) actually completed the study through the second follow-up telephone call."

[Item 6.1, Vol. 1.22, p. 89]

APPEARS THIS WAY
ON ORIGINAL

SUMMARY OF PATIENT DISPOSITION
ALL TREATED PATIENTS

	4% articaine HCl /1:100,000 epinephrine	2% lidocaine HCl/1:100,000 epinephrine	Total
All Randomized Patients	159	84	243
Randomized, Not Treated	1	0	1
All Treated Patients	158	84	242
Completed Study (CRF Checkbox)	139 (88%)	69 (82%)	208 (86%)
Discontinued Patients			
Protocol Deviation	17 (11%)	12 (14%)	29 (12%)
Patient lost to follow-up	1 (1%)	3 (4%)	4 (2%)
Other	1 (1%)	0	1 (<1%)

[Based on sponsor's Table 1, Vol. 1.22, p.113]

Seventeen articaine patients (11%) and 12 lidocaine patients (14%) had protocol deviations in this study. An additional patient in the articaine group, reported to have had an "other" reason for not having completed the study per protocol, and could not be contacted for his telephone interview until approximately 3 weeks after treatment.

[Item 6.2, Vol. 1.22, p. 89]

APPEARS THIS WAY
ON ORIGINAL

Summary of Patients with Protocol Deviations

Protocol Deviation	Treatment Group	Patient Numbers
Patient was found to have asthma	4% articaine/1:100,000 epinephrine	2339, 2341, 2546
	2% lidocaine/1:100,000 epinephrine	2325,2337
Follow-up telephone interview #2 was more than seven days after Treatment.	4% articaine/1:100,000 epinephrine	2340, 2479[a]
	2% lidocaine/1:100,000 epinephrine	2338, 2401
Follow-up telephone interview #2 was less than seven days after Treatment.	4% articaine/1:100,000 epinephrine	2272, 2280
Microbiology of urine was not performed	4% articaine/1:100,000 epinephrine	2014
Abnormal Laboratory Values[b]	4% articaine/1:100,000 epinephrine	2043, 2044, 2063, 2147, 2170
	2% lidocaine/1:100,000 epinephrine	2139, 2163
Premature Screening	2% lidocaine/1:100,000 epinephrine	2041
The dental procedure was started before measuring vital signs at 5 Minutes.	4% articaine/1:100,000 epinephrine	2472
Incorrect randomization	4% articaine/1:100,000 epinephrine	2272, 2276
	2% lidocaine/1:100,000 epinephrine	2325, 2469
Patient was breast feeding.		
	2% lidocaine/1:100,000 epinephrine	2493
Concomitant medications	4% articaine/1:100,000 epinephrine	2167[c], 2276[d]
Laboratory sample was lost by lab	4% articaine/1:100,000 epinephrine	2196
	2% lidocaine/1:100,000 epinephrine	2148,2176
No laboratory values	4% articaine/1:100,000 epinephrine	2274
	2% lidocaine/1:100,000 epinephrine	2194

"Extracted from Appendices 11.2.1 and 11.2.17

a Patient counted as "other" reason for not completing the study.

b Abnormal laboratory values included hematology and blood chemistry.
c Concomitant medication included the NSAID nabumetone within 24 hours prior to start of study.
d Concomitant medication included amitriptyline."
[based on sponsor's table, Vol.1.22, p.90]

Summary of Patient Demographics and Baseline Characteristics

Variable	Articaine (N=158)	Lidocaine (N=84)	P-Value
	Number (%) of Patients		
Sex			NS[a]
Male	78 (49)	33(39)	
Female	80 (51)	51 (61)	
Age			NS[a]
4 to < 13 years	3(2)	2 (2)	
≥ 13 years	155 (98)	82 (98)	
Mean ± SEM	33.7± 1.19	34.0± 1.56	
Range	4-77	9-74	
Weight (kg)			NS[b]
Mean ± SEM	71.3±1.13	67.9±1.62	
Range	16-105	23-118	
Race			NS[a]
White	143 (91)	80 (95)	
Black	6 (4)	3 (4)	
Asian	8 (5)	1 (1)	
Other	1 (1)	0	
Stratification			NS[a]
Simple Procedure	115 (73)	60 (71)	
Complex Procedure	43 (27)	24 (29)	
Supine systolic blood pressure (mmHg)			NS[b]
Mean ± SEM	121.2±1.60	120.0±2.31	
Range			
Supine diastolic blood pressure (mmHg)			NS[b]
Mean ± SEM	73.2±1.07	72.2±1.30	
Range			
Pulse Rate (bpm)			NS[b]
Mean ± SEM	79.4±1.13	78.2±1.61	
Range			
Respirations			NS[b]
Mean ± SEM	18.9±0.33	18.7±0.41	
Range			
Temperature (°C)			ND
Mean ± SEM	36.5±0.04	36.5±0.05	
Range			

Extracted from Table 2
NS No statistical significance ($p>0.05$)
ND Not determined
a Cochran-Mantel Haenszel test
b ANOVA
[based on sponsor's table, Item 7.2, Vol. 1.22, p. 93]

"Patients were stratified by procedure, either to the simple stratum (single extractions with no complications, routine operative procedures, single apical resections, and single crown procedures), or the complex procedure stratum (multiple extractions, multiple crowns and/or bridge procedures, multiple apical resections, alveolectomies, muco-gingival operations,

and other surgical procedures of the bone). In the articaine treatment group, 115/158 (73%) patients were stratified to the simple dental procedure group and 43 (27%) were stratified to the complex procedure group. In the lidocaine group 60/84 (71%) patients were stratified to the simple dental procedure group and 24 (29%) were stratified to the complex procedure group."

" One hundred and five (105/158, 66%) articaine patients presented with no relevant medical history at screening. Among the articaine patients, the most commonly reported medical conditions were allergy (13%), endocrine/metabolic (8%), gastrointestinal (7%), musculoskeletal (7%), and respiratory (6%). Sixty (60/84, 71%) lidocaine patients presented with no relevant medical history at screening. Among all lidocaine patients the most commonly reported medical conditions were endocrine/metabolic (10%), allergy (8%), genitourinary (6%), CNS/neurological (5%), and respiratory (5%)."

[Item 7.2, Vol. 1.22, p. 91]

Concomitant Medications

One hundred and twelve patients (112/158, 71%) patients in the articaine group and 55/84 (65%) patients in the lidocaine group received concomitant medications. The most common concomitant medications included paracetamol (36%, articaine; 31%, lidocaine), ibuprofen (13%, articaine; 17% lidocaine), estrogens (10%, articaine; 15%, lidocaine), beta-lactam antibacterials (10% articaine;11% lidocaine), hormonal contraceptives for systemic use (8%, articaine; 14% lidocaine), ands metronidazole (9%, articaine; 10% lidocaine). One patient in the articaine group received amitriptyline during the course of the study, a protocol violation. The patient experienced no clinically significant changes in vital signs and no adverse events on the day of treatment."

[Item 7.3, Vol. 1.22, p.94]

Section 7.2.1.5 Sponsor's Efficacy Results

"One hundred and fifty-seven (157) articaine patients and 84 lidocaine patients had observations for VAS scores of pain. Both treatment groups had low levels of pain during the dental procedures. (Of the two patients not included in the analysis, one was not treated and the other was lost to follow-up). The mean scores were similar across treatment groups for simple procedures and for complex procedures. However, in both treatment groups, scores for simple procedures were lower than scores for complex procedures and patient scores were higher than investigator scores. Among patients in the 4 to < 13 year age group, all three articaine patients and both lidocaine patients had low VAS scores for pain ($\leq$ 2.2 cm). There were no apparent differences in investigator or patient pain scores between simple and complex procedures in patients 4 to < 13 years of age. By the sponsor's analyses, 4% articaine HCl with 1:100,000 epinephrine has been shown to be no worse than 2% lidocaine HCl with 1:100,000 epinephrine with a $p > 0.05$.

A summary of VAS scores of pain stratified by dental procedure are presented in the table below.

[Item 7.4.1, Vol. 1.22, p.94]

APPEARS THIS WAY
ON ORIGINAL

A Summary of VAS Scores of Pain

	Pain Scores For All Treated Patients			
	Articaine		Lidocaine	
	Simple	Complex	Simple	Complex
All Patients				
N	114	43	60	24
Investigator Score (cm)				
Mean	0.3	0.4	0.2	0.4
Minimum				
Maximum				
Patient Score (cm)				
Mean	0.4	0.8	0.5	0.6
Minimum				
Maximum				
Patients 4 to < 13years				
N	2	1	1	1
Investigator Score (cm)				
Mean	0.0	0.0	0.0	2.2
Minimum				
Maximum				
Patient Score (cm)				
Mean	0.8	0.0	1.0	0.0
Minimum				
Maximum				
Patients ≥ 13years				
N	113	42	59	23
Investigator Score (cm)				
Mean	0.3	0.4	0.2	0.4
Minimum				
Maximum				
Patient Score (cm)				
Mean	0.4	0.8	0.5	0.6
Minimum				
Maximum				

Extracted from Tables 7.1 and 7.2
[based on sponsor's table, Item 7.4.1, Vol. 1.22, p. 95]

Adverse Events:

Adverse Events will be discussed in the safety review of this study

Section 7.2.1.6 Reviewer's Efficacy Discussion

The results of this study appear to indicate that, from a clinical perspective, the study drug is generally no less effective with respect to onset, duration, and pain relief than 2% lidocaine HCl with 1:100,000 epinephrine. The following comments should be noted:

In this pivotal equivalency trial, the sponsor has tried to show that there is no difference between their drug and the active control. For all three pivotal trials, the sponsor chose the primary efficacy variable of pain-measured on a VAS by pt. and investigator. By their analyses, 4% articaine HCl with 1:100,000 epinephrine has been shown to be no worse than 2% lidocaine HCl with 1:100,000 epinephrine with a $p > 0.05$.(We can say that the sponsor's efficacy results show no statistical significance indicating that it is unlikely to be any worse than the control drug.)

This stratification into categories of simple and complex procedures was done in response to Dr. Fred Hyman's (Dental Officer, HFD-540) suggestion in his review of June 28, 1996, in which he stated "Subjects should ideally be randomized and stratified according to the procedures being performed." This stratification suggestion was made to more accurately reflect the dose of articaine and the dental procedure for which it is being used. This, in turn, would allow for a more accurate comparison to the active control and also result in less confounding when comparing adverse events between groups for safety. Dr. Hyman also suggested, in his review, that a sample size of 1500 may be larger than necessary. I concur with Dr. Hyman's suggestions.

Changes made in Amendment #1 regarding statistical analysis were discussed with Dr. Chuanpu Hu (Biostat Reviewer, HFD-700) on 8-18-98 by this reviewer. Dr. Hu felt that the sponsor's changes to the analysis of treatment comparisons are more meaningful rather than less meaningful. Given that we expect a strata effect, the change in the amendment is probably more accurate. He also felt that any statistically significant differences are due to the large sample size only. I do not feel that these differences are of clinical significance.

Septanest (4% articaine HCl with 1:200,000 epinephrine) was not studied in this pivotal trial. It was, however, studied in a Phase 2 trial (S97001), which the sponsor considers a primary efficacy trial.

APPEARS THIS WAY
ON ORIGINAL

SECTION 7.2.2 STUDY 96001.02 US

Section 7.2.2 Protocol Synopsis

Title: A Single Dose Study to Evaluate the Safety and Efficacy of Septanest (4% articaine HCl) with 1:100.000 Epinephrine Versus 2% Lidocaine HCl with 1:100,000 Epinephrine in the Treatment of General Dental Procedures

Objective: "This single-dose , double blind, randomized, parallel group, multicenter, Phase III study is designed to demonstrate that 4% articaine HCl with 1:100,000 epinephrine is as safe as 2% lidocaine HCl with 1:100,000 epinephrine, both administered parenterally, when use in clinical dentistry. This study is also designed to show that 4% articaine with 1:100,000 epinephrine is efficacious."

[Item 2.0, Vol.1.26, p.283]

Study Design:

"This single-dose, double-blind, randomized, parallel -group, active-controlled, multicenter study will compare the safety and efficacy of 4% articaine HCl with 1:100,000 epinephrine versus 2% lidocaine HCl with 1:100,000 epinephrine administered parenterally. Twelve US sites will enroll approximately 88 patients (1056 total patients) to provide a total of 1000 completed patients. At each site, patients will be randomly be assigned in a 2:1 ratio, such that 666 completed patients (704 total patients) will receive articaine and 334 completed patients (352 total patients) will receive lidocaine."

Inclusion Criteria

Patients were to meet the following criteria to be eligible for participation in the study:

- Required infiltration anesthesia or nerve block anesthesia for any of the following: single extraction with no complications; multiple extractions; apical resections; alveolectomies; routine operative and crown and bridge procedures on vital teeth; and other routine procedures requiring oral local anesthesia In addition, patients who needed mucogingival operations and other surgical procedures on the bone when long-lasting ischemia and analgesia were required, were also eligible;
- Were between 4 and 80 years of age, inclusive;
- Must have had clinical laboratory values within normal range as determined by the reference laboratory;

Exclusion Criteria

Patients were to be excluded if they met any of the following:

- Had bony, fully impacted teeth or maxillo-facial surgery;
- Had any known or suspected allergies or sensitivities to sulfites or amide-type local anesthetics or any of the ingredients in the test solutions;
- Had concomitant cardiac or neurologic disease;
- Had a history of severe shock, paroxysmal tachycardia, frequent arrhythmia, severe untreated hypertension, or bronchial asthma;
- Were considered an inappropriate candidate for the study in the investigator's opinion due to a concomitant medical or psychiatric condition;
- Had evidence of soft tissue infection near the proposed injection site; but localized periapical or periodontal infections were permitted;
- Were taking monoamine oxidase (MAO) inhibitors, tricyclic antidepressants, phenothiazine, butyrophenones, vasopressor drugs, or ergot-type oxytocic drugs;
- Received chloroform, halothane, cyclopropane, trichloroethylene, or related anesthetics during the treatment visit;
- Were expected to require nitrous oxide or any general anesthesia;
- Had taken aspirin, acetaminophen, nonsteroidal anti inflammatory drugs (NSAIDs), or other analgesic agents within

24 hours prior to administration of study medication;

- Had previously participated in this study or had taken an investigational drug(s) or participated in another study within four weeks prior to initiation of treatment.

"The trial will consist of a screening visit, a treatment visit, and 2 follow-up telephone calls. At the screening visit, patients who meet all eligibility criteria and sign an informed consent form will provide a medical history and will have a brief physical examination, screening laboratory assessment and screening vital signs. Patients who meet all entry criteria will return for the treatment visit within the next eight days. At this time the patient will be randomized to one of two treatment groups . Baseline vital signs will be measured and study drug will then be administered. At one and five minutes following administration of the study drug, vital signs will again be obtained. Subsequently, the dental procedure will be performed followed by another measurement of vital signs and a brief physical examination. The patient will be asked to mark the level of pain experienced on a 10 cm Visual Analog Scale (VAS) with 0= no pain and 10=worst pain imaginable. A similar VAS will be used for the investigator evaluation. Any adverse events that occur during the treatment visit will be recorded by the investigator. The patient will then be discharged. Within 24 hours, a representative from the investigative site will telephone the patient to obtain a follow-up report of any adverse events that may have occurred after the patient was discharged. A second telephone call will be made 7 days after treatment to again obtain a follow-up report of any adverse events that may have occurred or persisted since the last follow-up call. All patients who receive study medication will be included in the safety evaluations of adverse events and vital signs. All patients randomized will be evaluated for efficacy."

[Item 3.0, Vol. 1.26, p.284]

"Although eight cartridges of study drug will be provided for each patient, the dose of study medication required for most procedures usually consists of one to three cartridges for adults and one cartridge for children. In more difficult cases, patients may require additional anesthesia. The additional anesthesia may be administered: however, dosages are not to exceed 7 mg/kg (3.2 mg/lb) of body weight. If a patient requires anesthesia in amounts greater than this he/she should be dropped from the study."

[Item 4.5, Vol. 1.26, p.288]

Figure 1 Study Schemata

DAYS: 1	2	3	4	5	6	7	8	9	10	11	12	13
VISIT: Screening (Day 1)							**Treatment (Day 8)**	**Follow-up #1 (Day 9)**			**Follow-up #2 (Day 13)**	
							Randomization Study Drug Admin. Dental Procedure VAS Pain Measurement AE Assessment	Telephone Call AE Assessment			Telephone-Call Call AE Assessment	

STUDY SCHEMATIC				
Procedure	**Screening Visit[a]**	**Treatment Visit**	**Follow-up #1 Telephone Call[b]**	**Follow-up #2 Telephone Call[c]**
Informed Consent Signed	X			
Complete Medical History	X			
Physical Examination	X	X[d]		
Clinical Laboratory Evaluation[e]	X			
Vital Signs	X	X[f]		
Recent/Concomitant Medications	X[g]	X	X	X
Randomization		X		
Study Drug Administration		X		
Drug Accountability		X		
Dental Procedure		X		
VAS Measurement of Pain[h]		X		
Adverse Event Assessment		X	X	X
Assessment of Persistent Numbness/Tingling of Mouth or Face			X	X

a Within eight days prior to the treatment visit.
b Within 24 hours following discharge from the site.
c Seven days following discharge from the site.
d Prior to study drug administration and following dental procedure.
e Includes a serum pregnancy test.
f Prior to administration of study drug, 1 and 5 minutes following study drug administration, and immediately following the dental procedure.
g All medications taken within 14 days prior to screening visit.
h To be completed by the patient and investigator independently.

[Item 7.0, Vol. 1.26, p.293]

Section 7.2.2.2 Statistical Analysis:

In this pivotal trial, which is an equivalency trial, the sponsor will try to show that there is no difference between their drug and the active control. The primary efficacy variable is the level of pain experienced during the dental procedure as measured on a VAS by both patient and investigator.

"A summary of patient characteristics, including age, race, sex, and weight, will be presented by treatment group for all patients who received study drug. Patients will be categorized by age into two groups of 1) 4 to < 13 years old and 2) $\geq$ 13 years old. Age and weight will be summarized by treatment group using descriptive statistics including mean, median, standard deviation, and range. Counts and percents of race and sex will be presented. Treatments will be compared for balance in age group, sex and race and strata using a Cochran-Mantel-Haenszel (CMH) test to adjust for center effects. Treatment comparisons of weight will be made with an analysis of variance (ANOVA) with treatment, center, strata,

treatment-by-center and treatment-by-strata, interaction effects. If the assumptions of normality are not met, appropriate normalizing transformations will be used."

"Descriptive statistics, including mean, median, standard deviation, and range, will be employed to summarize the total volume (mL) and the dose per unit of body weight (mg/kg) of study drug administered to patients by age group and strata."

[Items 9.1 and 9.2, Vol. 1.26 p.301]

Section 7.2.2.3 Protocol Amendments

"Two amendments were made to this protocol, one on December 20, 1996 and the second on July 14, 1997. One administrative change was made on January 24, 1997. Amendment No. 1 and the administrative change were made prior to the enrollment of any patients. Amendment 2 was made 4 months after the start of the study."

[Item 5, Vol. 1.26, p.23]

Amendment 1:

This amendment was dated 12-20-96. It consists of a change in protocol number, the Point of Contact, and new additional wording to the Objective, Randomization, Study Drug Administration, Drug Accountability, Inclusion Criteria, Exclusion Criteria, Vital Signs, Screening Evaluation, Adverse Events, Baseline Patient Characteristics, Dose Administered, Efficacy, Case Report Forms, Appendix A, Appendix C, and Appendix E sections of the protocol.

The Objective Section adds the sentence, "This study is also designed to show that 4% articaine 1:100,000 epinephrine is efficacious."

In the Randomization section, paragraph 2, after the phrase, "...the patient will be assigned to the next available patient number in ascending order", the following phrase was added, " if the procedure is from stratum 1 and the next available patient number in descending order if the procedure(s) is from stratum 2. A minimum of 25% of the patients will be assigned to stratum 2."

Added to the Study Drug Administration section, paragraph 2, "adults over 80", who, along with children under 8 will be prohibited from the study.

In the Drug Accountability section, the phrase was rewritten to say, "...used and partially used cartridges will be destroyed at the site..."

In the Inclusion Criteria section paragraphs 1 and 2, the phrase, "...and other routine procedures requiring local anesthesia." and the sentence "Must be $\geq$ than 8 and $\leq$ 80 years of age", were added.

The following Exclusion Criteria bullets were added:

- "Bony, fully impacted teeth or maxillo-facial surgery."
- "Must not be expected to require nitrous oxide, any topical or general anesthesia."

In the Vital Signs section, the term "two minutes" was added to indicate when standing blood pressure will be taken after the change from a supine position." The last two sentences of the second paragraph were rewritten as follows: " At one minute and five minutes following initial administration of study medication, the supine blood pressure, pulse and respiration will be taken. After completion of the dental procedure, the vital signs taken prior to study medication will be repeated except for temperature."

In the Screening Evaluation section, paragraph 2, the phrase was added, "...and must not be expected to require nitrous oxide, any topical or general anesthesia."

In the Adverse Events section, paragraph 3, the second sentence was rewritten to say, " Ā Bio-Pharm representative (see Section 8.3) must be contacted within one working day..." Also, a FAX number was added to the address for Bio-Pharm Clinical Services.

In the Patient Baseline Characteristics section the next to last sentence was rewritten to read, "Treatment comparisons of weight will be made with an analysis of variance (ANOVA) with treatment, center, strata, treatment-by-center and treatment-by-strata interaction effects."

The Dose Administered section was changed to indicate that descriptive statistics will be used to summarize the total volume and the dose per unit of body weight by strata as well as by age group.

In the Vital Signs section, the ANOVA was reworded to include strata, and treatment-by-center interaction.

In the Efficacy section, the first sentence was reworded as follows, " Treatment comparisons of patient and investigator VAS measurements will be made with an ANOVA with treatment, center, strata, treatment-by-center interaction and treatment-by-center interaction effects."

The following was added to the Case Report Forms section,"...Case report forms must be completed within one week from the patient's second follow-up interview."

Added to Appendix A was, "11. A signed W-9 form."

Appendix C paragraph 1 was reworded to, "Effective December 5th, 1996, the FDA issued new regulations pertaining to the elements required to an informed consent. Accordingly, a signed informed consent will be obtained from all subjects participating in this study or their legally authorized representative. This consent must be dated at the time it is signed. Case records including source documentation and case report forms must note the date the informed consent was signed and this date must be prior to any participation in this study. This consent must include the following items: "

Appendix E has new wording as follows, "4. To obtain valid informed consent from each patient who participates in the study. The date must be noted in the source documentation.

[Appendix F, Vol. 1.26, Pp.318-324]

Administrative Change # 1

These changes 1-24-97 after a meeting with the Agency:

On the sign off list , Suzanne Gagnon, M.D., Vice President, Medical Affairs was added and Spencer Hudson's title was changed to Vice President, Biometrics.

In the Introduction section the sentence was changed to read, "The study will be conducted in the United States (U.S.). "

In the Study Objective section the paragraph was reworded to, "This single-dose, double-blind, randomized, parallel -group, active-controlled, multicenter study will compare the safety and efficacy of 4% articaine HCl with 1:100,000 epinephrine versus 2% lidocaine HCl with 1:100,000 epinephrine administered parenterally. Twelve US sites will enroll approximately 88 patients (1056 total patients) to provide a total of 1000 completed patients. At each site, patients will be randomly be assigned in a 2:1 ratio, such that 666 completed patients (704 total patients) will receive articaine and 334 completed patients (352 total patients) will receive lidocaine."

The Number of Patients to be Studied section has been changed to, " Approximately 1056 patients will be enrolled into this study to provide 1000 completed patients; 666 patients will receive 4% articaine HCl with 1:100,000 epinephrine and 334 patients will receive 2% lidocaine HCl with 1:100,00 epinephrine. Patients from twelve sites in the U.S. will be enrolled in this study. In order to meet these enrollment goals, each of the twelve sites should attempt to enroll at least 88 patients."

The Sample Size section has been changed to, "The sample size for this study (1000 patients, 666 articaine and 334 lidocaine) is large enough to detect possible adverse events that occur at a rate of 1 in 100 in at least one articaine patient with a probability of 0.999 and at least one lidocaine patient with a probability of 0.97."

Appendix B, VAS Scale for Patients and Investigators has been changed to read, " Intermediate pain scales were deleted from the adult scale and a 'smiley face' VAS scale was added for patients 8 through 12 years of age, inclusive."

[Vol. 1.26, p. 325-326.]

Amendment #2

This amendment was dated 7-14-97 and includes the following changes:

In the Study Drug Administration section this sentence was reworded to, "For the purposes of this study, use in children under four and adults over 80 years of age is prohibited."

The Inclusion Criteria was changed to read:, "Must be $\geq$ 4 and $\leq$ 80 years of age."

Clinical Laboratory Evaluations and Serum Pregnancy Test section was changed to, "Clinical laboratory evaluations of all patients $\geq$ 13 years of age, including a serum pregnancy test for females of child bearing potential, will be completed at screening."

The Urinanalysis section has the new wording, " color/appearance, pH, specific gravity, bilirubin, blood, glucose, ketones, protein and microscopic examination for patients $\geq$ 13 years of age; dipstick measurements only for patients $\leq$ 12 years of age."

The Study Schematic section was rewritten as, "Clinical laboratory tests were footnoted as : Not Necessary for children $\leq$ 12 years of age."

The Screening Evaluation section now reads, "Clinical laboratory evaluations for all patients $\geq$ 13 years of age, including a serum pregnancy test for females of child bearing potential (see Section 6.3)."

The Baseline Patient Characteristics section has been changed to, "Patients will be categorized by age into two groups of 1) 4 to <13 years old and 2) $\geq$ 13 years old."

The section on VAS Scale for Patients and Investigator's has been reworded to, "Top VAS for Adults; bottom VAS for patients 4 through 12 years of age."

[Vol. 1.26, p.328]

Section 7.2.2.4 Conduct of Study

Patient Disposition:

"A total of 853 patients participated in this study. Five hundred sixty-nine (569) patients were randomized to receive articaine and 284 patients were randomized to receive lidocaine. Eight hundred and fifty-one patients (851, 99.8%) completed the study per protocol, 568 (99.8%0 in the articaine group and 283 (99.6%) in the lidocaine group. A total of two patients did not complete the study per protocol due to protocol deviations (1, < 1% articaine), and adverse events (1, ,1% lidocaine)."

[Item 6.1, Vol. 1.26, p.26]

SUMMARY OF PATIENT DISPOSITION
ALL TREATED PATIENTS

	4% Articaine HCl/ 1:100,000 Epinephrine	2% Lidocaine HCl/ 1:100,000 Epinephrine	Total
All Randomized Patients	569	284	853
All Treated Patients	569	284	853
Completed Study (CRF Checkbox)	568 (>99%)	283 (>99%)	851 (>99%)
Discontinued Patients			
Discontinued due to adverse event	0	1 (<1%)	1 (<1%)
Protocol Deviation	1 (<1%)	0	1(<1%)

[based on sponsor's Table 1, Vol. 1.26, p.48]

"Thirty-three articaine patients (6%) and 15 lidocaine patients (5%) had protocol deviations in this study. A summary of protocol deviations are presented in the table below."

Summary of Patients with Protocol Deviations

Protocol Deviation	Treatment Group	Number of Patients (%)
Patients took prohibited concomitant medications[a]	Articaine	24 (4)
	Lidocaine	10 (4)
Patients entered the study with asthma or a history of asthma	Articaine	8 (1)
	Lidocaine	4 (1)
Patient entered the study with an allergy to sulfites	Lidocaine	1 (<1)
Clinical laboratory tests not available[b]	Articaine	1 (<1)

Extracted from Appendices 11.2.2, 11.2.4, and 11.2.6
a concomitant medications included NSAIDS, acetylsalicylic acid, paracetamol, ibuprofen, amitriptyline, and fentanyl
b urinanalysis test not available

[Item 6.2, vol. 1.26, p.26]

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Summary of Patient Demographics and Baseline Characteristics

Variable	Articaine (N=569)	Lidocaine (N=284)	P-Value
	Number (%) of Patients		
Sex			NS[a]
Male	256 (45)	121(43)	
Female	313 (55)	163 (57)	
Age			NS[a]
4 to < 13 years	1(<1)	1 (<1)	
≥ 13 years	568 (>99)	283 (>99)	
Mean ± SEM	38.9± 0.60	38.7± 0.87	
Range	10-79	12-77	
Weight (kg)			NS[b]
Mean ± SEM	75.4±0.72	74.1±1.00	
Range	42.7-139.5	43.2-150.9	
Race			NS[a]
White	429 (75)	214 (75)	
Black	54 (9)	28 (10)	
Asian	28 (5)	20 (7)	
Hispanic	42 (7)	15 (5)	
Other	16 (3)	7 (2)	
Stratification			NS[a]
Simple Procedure	427 (75)	211 (74)	
Complex Procedure	142 (25)	73 (26)	
Supine systolic blood pressure (mmHg)			NS[b]
Mean ± SEM	122.4±0.67	122.2±0.90	
Range			
Supine diastolic blood pressure (mmHg)			NS[b]
Mean ± SEM	74.7±0.42	74.5±0.59	
Range			
Pulse Rate (bpm)			NS[b]
Mean ± SEM	71.8±0.51	72.7±0.67	
Range			
Respirations			NS[b]
Mean ± SEM	16.8±0.14	16.6.±0.19	
Range			
Temperature (°C)			ND
Mean ± SEM	36.6±0.02	36.6±0.03	

Extracted from Table 2
NS No statistical significance ($p>0.05$)
ND Not determined
a Cochran-Mantel Haenszel test
b ANOVA
c N=568 (articaine); N=281 lidocaine)
d N=567 (articaine); N=284 (lidocaine)
[based on sponsor's table, Item 7.2, Vol. 1.26, p. 29]

"Patients were stratified by procedure, either to the simple stratum (single extractions with no complications, routine operative procedures, single apical resections, and single crown procedures), or the complex procedure stratum (multiple extractions, multiple crowns and/or bridge procedures, multiple apical resections, alveolectomies, muco-gingival operations,

and other surgical procedures of the bone). In the articaine treatment group, 427/569 (75%) patients were stratified to the simple dental procedure group and 142 (25%) were stratified to the complex procedure group. In the lidocaine group, 211/284 (74%) patients were stratified to the simple dental procedure group and 73 (26%) were stratified to the complex procedure group."

" Two hundred seventy-five (275/569, 48%) articaine patients presented with no relevant medical history at screening. Among the articaine patients, the most commonly reported medical conditions were allergy (22%), musculoskeletal (13%), cardiovascular (12%), genito-urinary (9%), and endocrine/metabolic (8%). One hundred thirty-six (136/284, 48%) lidocaine patients presented with no relevant medical history at screening. Among all lidocaine patients the most commonly reported medical conditions were allergy (18%), cardiovascular (13%), genito-urinary (12%), , musculoskeletal (10%), endocrine/metabolic (7%), and gastrointestinal (7%)."

[Item 7.2, Vol. 1.26, p.27]

Concomitant Medications

"Three hundred and forty-five patients (345/569, 61%) patients in the articaine group and 175/284 (62%) patients in the lidocaine group received concomitant medications. The most common concomitant medications included paracetamol (17%, articaine; 18%, lidocaine), ibuprofen (14%, articaine; 15% lidocaine), estrogens (14%, articaine; 18%, lidocaine), hormonal contraceptives for systemic use (11%, articaine; 15% lidocaine), and hydrocodone bitartrate (8%, articaine; 8% lidocaine). Approximately 5% each of articaine and lidocaine patients received one of the following medications within 24 hours prior to the dental procedure: NSAIDS, acetyl salicylic acid, paracetamol, ibuprofen, fentanyl, and amitriptyline."

[Item 7.3, Vol. 1.26, p. 30]

Section 7.2.2.5 Sponsor's Efficacy Results

"All five hundred and sixty-nine (569) articaine patients and 283/284 lidocaine patients had observations for VAS scores of pain. Overall, both treatment groups had low mean levels of pain during the dental procedures. The mean scores were similar across treatment groups for simple procedures ($\leq$ 0.8 cm). However, in both treatment groups, mean scores for simple procedures were the same as or lower than scores for complex procedures and in three of four cases, mean patient scores were higher than investigator scores. Among patients in the 4 to < 13 year age group, both the articaine patient an the lidocaine patients had low VAS scores for pain. There were no differences between the investigator and patient pain scores, in patients 4 to < 13 years of age. Among patients $\geq$ 13years of age, mean patient scores were slightly higher than mean investigator scores for both treatment groups with the exception of the complex stratum, articaine group, but all means were $\leq$ 0.8 cm."

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A Summary of VAS Scores of Pain

	Pain Scores For All Treated Patients			
	Articaine		Lidocaine	
	Simple	Complex	Simple	Complex
All Patients				
N	427	142	211	72
Investigator Score (cm)				
Mean	0.4	0.6	0.5	0.7
Minimum				
Maximum				
Patient Score (cm)				
Mean	0.5	0.5	0.6	0.8
Minimum				
Maximum				
Patients 4 to < 13years				
N	1	0	1	0
Investigator Score (cm)	0.2	-	0.5	-
Patient Score (cm)	0.2	-	0.5	-
Patients ≥ 13years				
N	426	142	210	23
Investigator Score (cm)				
Mean	0.4	0.6	0.5	0.4
Minimum				
Maximum				
Patient Score (cm)				
Mean	0.5	0.5	0.6	0.6
Minimum				
Maximum				

"Extracted from Tables 7.1 and 7.2"
[based on sponsor's table, Item 7.4.1, Vol. 1.26, p.31]

Adverse Events:

Adverse Events will be discussed in the safety review of this study.

Section 7.2.2.6 Reviewer's Efficacy Discussion

Here too, the results of this study appear to indicate that, from a clinical perspective, the study drug is generally no less effective with respect to onset, duration, and pain relief than 2% lidocaine HCl with 1:100,000 epinephrine. The foliowing comments should be noted:

As with the previous pivotal equivalency trial, the sponsor has tried to show that there is no difference between their drug and the active control. For all three pivotal trials, the sponsor chose the primary efficacy variable of pain-measured on a VAS by pt. and investigator. By their analyses, 4% articaine HCl with 1:100,000 epinephrine has been shown to be no worse than 2% lidocaine HCl with 1:100,000 epinephrine with a $p > 0.05$.

This stratification into categories of simple and complex procedures was done in response to Dr. Fred Hyman's (Dental Officer, HFD-540) suggestion in his review of June 28, 1996, in which he stated "Subjects should ideally be randomized and stratified according to the procedures being performed." This stratification suggestion was made to more accurately reflect the dose of articaine and the dental procedure for which it is being used. This, in turn, would allow for a more accurate comparison to the active control and also result in less confounding when comparing adverse events between groups for safety. Dr. Hyman also suggested, in his review, that a sample size of 1500 may be larger than necessary. I concur with Dr. Hyman's suggestions.

Changes made in Amendment #1 regarding statistical analysis were discussed with Dr. Chuanpu Hu (Biostat Reviewer, HFD-700) on 8-18-98 by this reviewer. Dr. Hu felt that the sponsor's changes to the analysis of treatment comparisons are more meaningful rather than less meaningful. Given that we expect a strata effect, the change in the amendment is probably more accurate. He also felt that any statistically significant differences are due to the large sample size only. I do not feel that these differences are of clinical significance.

Septanest — 4% articaine HCl with 1:200,000 epinephrine) was not studied in this pivotal trial. It was, however, studied in a Phase 2 trial (S97001) which the sponsor considers a primary efficacy trial.

Further the proposed draft labeling in the **INDICATIONS AND USAGE SECTION** states that Septanest — d Septanest — are indicated for, ".. ——————— " ——— surgery was not studied in this trial and therefore this indication should not be included in the labeling.

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SECTION 7.2.3 STUDY 96002.01 US

Section 7.2.3.1 Protocol Synopsis

Title: A Single Dose Study to Evaluate the Safety and Efficacy of 4% Articaine HCl with 1:100.000 Epinephrine Versus 2% Lidocaine HCl with 1:100,000 Epinephrine in the Treatment of General Dental Procedures

Objective: "This single-dose , double blind, randomized, parallel group, multicenter, Phase III study is designed to demonstrate that 4% articaine HCl with 1:100,000 epinephrine is as safe as 2% lidocaine HCl with 1:100,000 epinephrine, both administered parenterally, when use in clinical dentistry. This study is also designed to show that 4% articaine with 1:100,000 epinephrine is efficacious.

[Item 2.0, Vol. 1.36, p.158]

Study Design:

"This single-dose, double-blind, randomized, parallel -group, active-controlled, multicenter study will compare the safety and efficacy of 4% articaine HCl with 1:100,000 epinephrine versus 2% lidocaine HCl with 1:100,000 epinephrine administered parenterally. At least eight U.S. sites will enroll a total of 210 patients including approximately 42 children between 4 and 12 years of age, inclusive. At each site, patients will be randomly be assigned in a 2:1 ratio, such that 140 patients (including 28 children) will receive articaine and 70 patients (including 14 children) will receive lidocaine.

Inclusion Criteria

- Must have the need for infiltration anesthesia or nerve block anesthesia for any of the following: single extraction with no complications; multiple extractions; apical resections; alveolectomies; routine operative and crown and bridge procedures on vital teeth and other routine procedures requiring oral local anesthesia. In addition, patients who need muco-gingival operations and other surgical procedures on the bone when long lasting ischaemia and analgesia are required are also eligible for study entry.
- Must be ≥4 and ≤80 years of age.

Exclusion Criteria

- Bony, fully impacted teeth or maxillo-facial surgery
- Must not have any known or suspected allergies or sensitivities to sulfites or amide-type local anesthetics or any of the ingredients in the test solutions (see Section 4.1).
- Must not have concomitant cardiac or neurologic disease.
- Must not have severe shock, paroxysmal tachycardia, frequent arrhythmia, severe untreated hypertension, or bronchial asthma.
- Must not in the investigator's opinion, be considered an inappropriate candidate for the study due to a concomitant medical or psychiatric condition.
- Must not have evidence of soft tissue infection near the proposed injection site. Localized periapical or periodontal infections are permitted,
- Must not be taking MAO inhibitors, tricyclic antidepressants, phenothiazine, butyrophenones, vasopressor drugs, or ergot-type oxytocic drugs.

- Must not receive chloroform, halothane, cyclopropane, trichloroethylene, or related anesthetics during

the treatment visit.

- Must not be expected to require nitrous oxide, any topical or general anesthesia.
- Must not have taken aspirin, acetaminophen. NSAIDS or other analgesic agents within 24 hours prior to administration of study medication.
- Must not have previously participated in this study and must not have taken an investigational drug(s) or participated in another study within four weeks prior to initiation of treatment.

[Item 5.2, Vol. 1.36, pp. 9-10]

The trial will consist of a screening visit, a treatment visit, and 2 follow-up telephone calls. At the screening visit, patients who meet all eligibility criteria and sign an informed consent form will provide a medical history and will have a brief physical examination, screening laboratory assessment and screening vital signs. Patients who meet all entry criteria will return for the treatment visit within the next eight days. At this time the patient will be randomized to one of two treatment groups . Baseline vital signs will be measured and study drug will then be administered. At one and five minutes following administration of the study drug, vital signs will again be obtained. Subsequently, the dental procedure will be performed followed by another measurement of vital signs and a brief physical examination. The patient will be asked to mark the level of pain experienced on a 10 cm Visual Analog Scale (VAS) with 0= no pain and 10=worst pain imaginable. A similar VAS will be used for the investigator evaluation. Any adverse events that occur during the treatment visit will be recorded by the investigator. The patient will then be discharged. Within 24 hours, a representative from the investigative site will telephone the patient to obtain a follow-up report of any adverse events that may have occurred after the patient was discharged. A second telephone call will be made 7 days after treatment to again obtain a follow-up report of any adverse events that may have occurred or persisted since the last follow-up call. All patients who receive study medication will be included in the safety evaluations of adverse events and vital signs. All patients randomized will be evaluated for efficacy."

[Item 3.0, Vol. 1.36, p. 159]

"Although four cartridges of study drug will be provided for each patient, the dose of study medication required for most procedures usually consists of one to three cartridges for adults and one cartridge for children. In more difficult cases, patients may require additional anesthesia. The additional anesthesia may be administered: however, dosages are not to exceed 7 mg/kg (3.2 mg/lb) of body weight. If a patient requires anesthesia in amounts greater than this he/she should be dropped from the study."

[Item 4.5, Vol. 1.36, p.163]

Figure 1 Study Schemata

DAYS: 1	2	3	4	5	6	7	8	9	10	11	12	13
VISIT: Screening (Day 1)						Treatment (Day 8)		Follow-up #1 (Day 9)			Follow-up #2 (Day 13)	
						Randomization Study Drug Admin. Dental Procedure		Telephone Call AE Assessment			Telephone-Call Call AE Assessment	

VAS Pain Measurement
AE Assessment

STUDY SCHEMATIC				
Procedure	**Screening Visit[a]**	**Treatment Visit**	**Follow-up #1 Telephone Call[b]**	**Follow-up #2 Telephone Call[c]**
Informed Consent Signed	X			
Complete Medical History	X			
Physical Examination	X	X[d]		
Clinical Laboratory Evaluation[e] and Urine Pregnancy Test	X			
Vital Signs	X	X[f]		
Randomization		X		
Study Drug Administration		X		
Drug Accountability		X		
Dental Procedure		X		
VAS Measurement of Pain[g]		X		
Adverse Event Assessment		X	X	X
Assessment of Persistent Numbness/Tingling of Mouth or Face			X	X

a Within eight days prior to the treatment visit.
b Within 24 hours following discharge from the site.
c 7 days following discharge from the site.
d Prior to study drug administration and following dental procedure.
e Not necessary for children ≤ 12 years of age.
f To be conducted at the following times: prior to administration of study drug, one minute following study study drug administration, five minutes following study drug administration, and immediately following the dental procedure.
g To be completed by the patient and investigator independently.

[Vol. 1.36, p.168]

Section 7.2.3.2 Statistical Analysis:

In this pivotal trial, which is an equivalency trial, the sponsor will try to show that there is no difference between their drug and the active control. The primary efficacy variable is the level of pain experienced during the dental procedure as measured on a VAS by both patient and investigator.

"A summary of patient characteristics, including age, race, sex, and weight, will be presented by treatment group for all patients who received study drug. Patients will be categorized by age into two groups of 1) 4 to less than 13 years old and 2) equal to or greater than 13 years old. Age and weight will be summarized by treatment group using descriptive statistics including mean, median, standard deviation, and range. Counts and percents of race and sex will be presented. Treatments

will be compared for balance in age group, sex and race and strata using a Cochran-Mantel-Haenszel (CMH) test to adjust for center effects. Treatment comparisons of weight will be made with an analysis of variance (ANOVA) with treatment, center, strata, treatment-by-center and treatment-by-strata, interaction effects. If the assumptions of normality are not met, appropriate normalizing transformations will be used."

"Descriptive statistics, including mean, median, standard deviation, and range, will be employed to summarize the total volume (mL) and the dose per unit of body weight (mg/kg) of study drug administered to patients by age group and strata."

[Items 9.1 and 9.2, Vol. 1.36 p. 156]

Section 7.2.3.3 Protocol Amendments

"One amendment was made to this protocol, on October 24, 1997, 11 days after the start of the study.

Amendment 1:
This amendment was dated 10-24-97. It consists of a change in protocol number, Inclusion Criteria, Clinical Laboratory Evaluations and Serum Pregnancy Test, Study Procedures, and Screening Evaluation.

The new wording for the Protocol Number and date is, "Protocol No. S96002.01 Amendment Date No.1, October 24, 1997."

The Inclusion Criteria has been reworded to, "Females of child bearing potential must have a negative urine pregnancy test", and the following sentence has been deleted, "Must have clinical laboratory values within 15% (above or below) of the normal range ass determined by the reference laboratory (see Section 6.2)."

The Clinical Laboratory Evaluations and Serum Pregnancy Test will now read, "Clinical laboratory evaluations for all patients $\geq$ 13 years of age will be performed at screening. All laboratory values will serve as a baseline at the end of the study for any adverse event indicating a possible laboratory abnormality. The urine pregnancy test must be negative for a patient to be eligible for study participation." The other new wording in this section will be, "dipstick measurements will be performed for all patients, including those $\leq$ 12 years of age."

Under Study Procedures, the new sentence will be, "Urine pregnancy test to be performed."

In the Screening Evaluation section the phrase has been changed to, " urine pregnancy test for females of child bearing potential."

[Appendix F, Vol. 1.36, pp. 193-194.]

Section 7.2.3.4 Conduct of Study

Patient Disposition:

"A total of 230 patients participated in this study. On hundred and fifty-five (155) patients were randomized to receive articaine and 75 patients were randomized to receive lidocaine. Two hundred and twenty-eight (228) patients (99%) completed the study per protocol, 155 (100%) in the articaine group and 73 (97%) in the lidocaine group. A total of 2 patients, both in the lidocaine group, did not complete the study as they were lost to follow-up (3% lidocaine)."

[Item 6.1, Vol. 1.36, p. 25]

SUMMARY OF PATIENT DISPOSITION
ALL TREATED PATIENTS

	4% articaine HCl /1:100,000 epinephrine	2% lidocaine HCl/1:100,000 epinephrine	Total
All Randomized Patients	155	75	230
All Treated Patients	155	75	230
Completed Study (CRF Checkbox)	155 (100%)	73 (97%)	228 (99%)
Discontinued Patients			
Protocol Deviation	13 (8%)	6 (8%)	19 (8%)
Patient lost to follow-up	0	2 (3%)	2(1%)

[Based on sponsor's Table 1, Vol. 1.36, p.46]

"Thirteen articaine patients (8%) and 6 lidocaine patients (8%) had protocol deviations in this study. Because the investigators assigned patients to either the simple or complex stratum according to their clinical judgment, assignments that did not always strictly follow the guidelines ... were not considered protocol violations. A summary of protocol deviations is presented in the following table."

[Item 6.2, Vol. 1.36, p.25]

Summary of Patients with Protocol Deviations

Protocol Deviation	Treatment Group	Patient Numbers
Patient incorrectly randomized	Lidocaine	3109B-E[a]
Patients took prohibited concomitant medications[b]	Articaine	3002, 3020, 3021, 3023, 3041 3067,3078
	Lidocaine	3037
Patients entered the study with asthma or a history of asthma	Articaine	3010, 3103
	Lidocaine	3100
Patient Pregnant	Articaine	3227
Missing one or both telephone interviews	Lidocaine	3017, 3109/B-E
No laboratory data (sample hemolyzed or lost)	Articaine	3194
	Lidocaine	3158, 3226
No temperature at screening	Articaine	3018
Received greater than the maximum recommended dose of 7 mg/kg articaine	Articaine	3099

Extracted from Appendices 1.2.4, 11.2.6 and 11.2.18.
a two patients have number 3109 (3109/A-T and 3109/B-E); patient 3109/B-E received study medication remaining from patient 3109/A-T.
b concomitant medications included indomethacin, acetylsalicylic acid, paracetamol, hydrocodone, ibuprofen.

[based on sponsor's table, Item 6.2, Vol. 1.36, p.26]

Summary of Patient Demographics and Baseline Characteristics

Variable	Articaine (N=155)	Lidocaine (N=75)	P-Value
	Number (%) of Patients		
Sex			0.037[a]
Male	84 (54)	30 (40)	
Female	71 (46)	51 (60)	
Age			NS[a]
4 to < 13 years	46 (30)	17 (23)	
≥ 13 years	109 (70)	58 (77)	
Mean ± SEM	29.1± 1.43	31.0± 2.01	
Range	4-79	5-71	
Weight (kg)[c]			NS[b]
Mean ± SEM	62.1±1.83	62.1±2.61	
Range	18.2-145.5	15.9-122.7	
Race			NS[a]
White	75 (48)	36 (48)	
Black	14 (9)	3 (4)	
Asian	8 (5)	6 (8)	
Hispanic	52 (34)	27 (36)	
Other	6 (4)	3 (4)	
Stratification			NS[a]
Simple Procedure	133 (86)	67 (89)	
Complex Procedure	22 (14)	8 (11)	
Supine systolic blood pressure (mmHg)			0.004[b]
Mean ± SEM	115.6±1.31	115.1±1.88	
Range			
Supine diastolic blood pressure (mmHg)			NS[b]
Mean ± SEM	74.2±.96	75.0±1.35	
Range			
Standing systolic blood pressure (mmHg)			0.009[b]
Mean ± SEM	119.1±1.33	117.3±1.71	
Range			
Standing diastolic blood pressure (mmHg)			NS[b]
Mean ± SEM	76.2±0.89	77.9±1.35	
Range			
Pulse Rate (bpm)			NS[b]
Mean ± SEM	76.6±0.88	75.8±1.55	
Range			
Respirations			NS[b]
Mean ± SEM	17.0±0.26	16.9±0.36	
Range			
Temperature (°C)			ND
Mean ± SEM	36.6±0.04	36.6±0.05	
Range			

Extracted from Tables 2 and 8.1

NS No statistical significance (p>0.05)

ND Not determined

a Cochran-Mantel Haenszel test

b ANOVA
c N=153 (articaine) ; N=73 (lidocaine)
d N=154 (articaine) ; N=75 (lidocaine)"
[based on sponsor's table, Item 7.2, Vol. 1.36, p. 28]

"Patients were stratified by procedure, either to the simple stratum (single extractions with no complications, routine operative procedures, single apical resections, and single crown procedures), or the complex procedure stratum (multiple extractions, multiple crowns and/or bridge procedures, multiple apical resections, alveolectomies, muco-gingival operations, and other surgical procedures of the bone). In the articaine treatment group, 133/155 (86%) patients were stratified to the simple dental procedure group and 22 (14%) were stratified to the complex procedure group. In the lidocaine group 67/75 (89%) patients were stratified to the simple dental procedure group and 8 (11%) were stratified to the complex procedure group."

" One hundred and thirteen (113/155, 73%) articaine patients presented with no relevant medical history at screening. Among the articaine patients, the most commonly reported medical conditions were allergy (8%), genito-urinary (6%), CNS/neurological (5%) and cardiovascular (5%). Forty-nine (49/75, 65%) lidocaine patients presented with no relevant medical history at screening. Among all lidocaine patients the most commonly reported medical conditions were genito-urinary 12%), CNS/neurological (5%), cardiovascular (5%), and gastrointestinal (5%)."

[Item 7.2, Vol. 1.36, p. 27]

Concomitant Medications

Forty-eight (48/155, 31%) patients in the articaine group and 25/74 (33%) patients in the lidocaine group received concomitant medications. The most common concomitant medications included paracetamol (10%, articaine; 11%, lidocaine), ibuprofen (10%, articaine; 7% lidocaine), and hydrocodone bitartrate (5% articaine; 8% lidocaine). A total of 5% (7/155) of articaine and 1% (1/75) of lidocaine patients received one or more of the following medications within 24 hours prior to the dental procedure: indomethacin, acetylsalicylic acid, paracetamol, hydrocodone, or ibuprofen."

[Item 7.3, Vol. 1.36, p.29]

Section 7.2.3.5 Sponsor's Efficacy Results

"One hundred and fifty-five (155) articaine patients and 75 lidocaine patients has observations for VAS scores of pain. Overall, both treatment groups had low levels of pain during the dental procedures. The mean scores were similar across treatment groups for simple procedures ($\leq$ 0.5 cm) and for complex procedures ($\leq$ 1.0 cm). However, in both treatment groups, mean scores for simple procedures were lower than scores for complex procedures and mean patient scores were higher than investigator scores. There were no statistically significant (Kruskal-Wallis test) differences between treatment groups in median investigator (articaine and lidocaine groups: 0.0 for simple and 0.2 for complex) and patient (articaine group: 0.0 for simple , 0.2 for complex; lidocaine group 0.0 for simple , 0.3 for complex) scores (Table 7.1). When analyzed by age group, trends for mean VAS scores in each age group were similar to those observed for the overall population. A summary of VAS scores of pain stratified by dental procedure is presented in the following table..

[Item 7.4.1, Vol. 1.36, pp.29-30.]

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A Summary of VAS Scores of Pain

	Pain Scores For All Treated Patients			
	Articaine		Lidocaine	
	Simple	Complex	Simple	Complex
All Patients				
N	133	22	67	8
Investigator Score (cm)				
Mean	0.2	0.4	0.3	0.8
Minimum				
Maximum				
Patient Score (cm)				
Mean	0.4	0.8	0.5	1.0
Minimum				
Maximum				
Patients 4 to < 13years				
N	40	6	16	1
Investigator Score (cm)				
Mean	0.4	0.8	0.3	3.4
Minimum				
Maximum				
Patient Score (cm)				
Mean	0.5	1.3	0.7	4.5
Minimum				
Maximum				
Patients ≥ 13years				
N	93	16	51	7
Investigator Score (cm)				
Mean	0.2	0.3	0.3	0.4
Minimum				
Maximum				
Patient Score (cm)				
Mean	0.3	0.6	0.5	0.5
Minimum				
Maximum				

"Extracted from Tables 7.1 and 7.2" [based on sponsor's table, Item 7.4.1, Vol. 1.36, p. 30]

Adverse Events:

Adverse Events will be discussed in the safety review of this study.

Section 7.2.3.6 Reviewer's Efficacy Discussion

The results of this third study also appear to indicate that, from a clinical perspective, the study drug is generally no less effective with respect to onset, duration, and pain relief than 2% lidocaine HCl with 1:100,000 epinephrine. The following comments should be noted:

In this pivotal equivalency trial, the sponsor has tried to show that there is no difference between their drug and the active control. For all three pivotal trials, the sponsor chose the primary efficacy variable of pain-measured on a VAS by pt. and

investigator. By their analyses, 4% articaine HCl with 1:100,000 epinephrine has been shown to be no worse than 2% lidocaine HCl with 1:100,000 epinephrine with a $p > 0.05$.

This stratification into categories of simple and complex procedures was done in response to Dr. Fred Hyman's (Dental Officer, HFD-540) suggestion in his review of June 28, 1996, in which he stated "Subjects should ideally be randomized and stratified according to the procedures being performed." This stratification suggestion was made to more accurately reflect the dose of articaine and the dental procedure for which it is being used. This, in turn, would allow for a more accurate comparison to the active control and also result in less confounding when comparing adverse events between groups for safety. Dr. Hyman also suggested, in his review, that a sample size of 1500 may be larger than necessary. I concur with Dr. Hyman's suggestions.

Septanest— 4% articaine HCl with 1:200,000 epinephrine) was not studied in this pivotal trial. It was, however, studied in a Phase 2 trial (S97001) which the sponsor considers a primary efficacy trial.

The proposed draft labeling in the **INDICATIONS AND USAGE SECTION** states that Septanest— nd Septanest— are indicated for, "... surgery was not studied in this trial and therefore this indication should not be listed in the labeling.

SECTION 7.2.4 OTHER SUPPORTING CLINICAL TRIALS

Section 7.2.4.1 Study S97001

This efficacy study measured onset, depth, and duration of anesthesia using electrical stimulation of the dental pulp.

"This was a single and multiple dose, open, non-randomized single center efficacy and phamacokinetic study in 20 (10M/10F) normal healthy volunteers using 4% articaine HCl 1:200,000 epinephrine, single dose (1.7mL) and multiple dose(5.1mL). For the primary efficacy evaluation , subjects underwent electric pulp testing to determine the time on onset and duration of anesthesia."

Reviewer's note: An electric pulp tester is a device used in the dental office to determine the vitality of pulpal tissue in a tooth or the depth of anesthesia in a specific tooth. It is placed on the tooth and a small electrical current is passed through the tooth. This current is gradually increased until the patient feels a tingling sensation in the tooth and which point the test is stopped and a numerical read-out (usually numbers from 0 to 10) is recorded from the dial which was used to increase the current. A reading of 10 would indicate profound anesthesia or a non-vital pulp.

"Ten (10, 50%) of the 20 treated subjects were male and 10 (50%) were female. The mean age of all subjects was 32.6 years (range; 23-48 years). The mean weight of all subjects was 70.7 kg (range: 52.7 to 88.2 kg). Twelve (12, 60 %) of the subjects were Hispanic, 5 (25%) were White and 3(15%) were Black."

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Patient Demography, S97001

		4% Articaine HCl with 1:200,000 Epinephrine
Total No. of Treated Subjects		20
Age (yrs)	Mean ± SEM	32.6±1.69
	Range	23-48
Weight (kg)	Mean ± SEM	74.5±0.62
	Range	52.7-88.2
Sex N (%)	Female	10 (50%)
	Male	10 (50%)
Race N (%)	White	5 (25%)
	Black	3 (15%)
	Hispanic	12 (60%)

"Twenty patients were evaluated for efficacy after receiving 1.7 mL (1 cartridge; 68 mg of articaine HCl) of study medication (4 % articaine HCl with 1:200,000 epinephrine) on Day 0."

"The onset, duration, and depth of anesthesia were determined by electric pulp stimulation following a single injection of 4% articaine HCl with 1:200,000 epinephrine, 1.7 mL."

"The onset of anesthesia was rapid, ranging from — minutes with a mean time of 3.65±0.393 minutes. The duration of anesthesia ranges from —— minutes, with a mean time of 68.20±8.265 minutes."

Onset and Duration of Anesthesia Following Administration of Septanest N, S97001

	Onset of Anesthesia (mean ±SEM, minutes)	Duration of Anesthesia (mean±SEM, minutes)
All Patients (n=20)	3.65±0.393	68.20±8.265
White (n=5)	3.80±0.860	58.00±10.909
Black (n=3)	5.00±1.00	112.00±39.230
Hispanic (n=12)	3.25±0.479	61.50±7.551
Female (n=10)	3.00±0.471	68.30±15.033
Male (n=10)	4.30±0.578	68.10±7.899

"Anesthesia was complete in 100% of patients."
[Vol. 1.40, pp. 33-34.]

Section 7.2.4.2 Supportive Clinical Studies France A and France B

Both France A and France B were randomized, single blind parallel-group, active controlled , single center studies. Both studies were under the direction of J.M. Vaillant.

"In study France A, 51 subjects (33% male, and 66% female) were randomized to receive Septanest — and 49 subjects (37% male, 63% female) were randomized to receive Alphacaine SP, both with 1:100,000 epinephrine. In study France B 50 subjects (46% male, 54% female) were randomized to receive Septanest — and 50 subjects (44% male, 56% female) were randomized to receive Alphacaine N, both with 1:200,000 epinephrine. The formulations of Septanest used in these trials differed slightly from the formulation proposed for marketing in the United States, in that they contained a higher concentration of sodium metabisulfite and also contained sodium edetate."

[Item 6.6, Vol. 1.40, p.40]

Patient Characteristics, Studies France A and France B

	Septanest — 4% articaine HCl with 1:100,000 epinephrine	Alphacaine SP 4% articaine HCl with 1:100,000 epinephrine	Septanest — 4% articaine HCl with 1:200,000 epinephrine	Alphacaine N 4% articaine HCl with 1:200,000 epinephrine
Males				
N	17	18	23	22
Mean Age (yrs.)	33.2	30.3	27.2	28.4
Females				
N	34	31	27	28
Mean Age (yrs.)	22.5	25.2	25.8	27.4
Total N	51	49	50	50

"Extracted from Study Reports France A and France B, Section 8.4.3 Vol. 1.39, p301,363."

[Item 6.6, Vol. 1.40, p 40.]

"In France A, the mean initial dose of Septanest —nd Alphacaine SP , both 1:100,000 epinephrine, were similar for both mandibular block, slightly less than 4 mL) and maxillary infiltration (slightly more than 2 mL). In France B, with 1:200,000 epinephrine, mean initial doses were higher for Septanest— than for Alphacaine N for both routes of injection. The need for reinjection of anesthetic during the procedure was low in France A, but in France B about a third of all patients required more anesthetic during the procedure. The average waiting time was comparable for Septanest and Alphacaine, being 2.0 minutes in France A (1:100,000 epinephrine) and 4.58-4.23 minutes in France B (1:200,000 epinephrine)."

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Evaluation of Effectiveness in Supportive Clinical Trials, France A and France B

	France A		France B	
	Septanest 4% articaine HCl with 1:100,000 epinephrine	Alphacaine SP 4% articaine HCl with 1:100,000 epinephrine	Septanest 4% articaine HCl with 1:200,000 epinephrine	Alphacaine N 4% articaine HCl with 1:200,000 epinephrine
Number of Subjects	51	49	50	50
Mean initial dose, mL				
Mandibular	3.73	3.97	4.38	3.64
Maxillary	2.18	2.32	3.38	2.66
Additional dose at start of procedure				
No. of subjects	4	5	1	4
Mean, mL	1.32	1.50	n.r.	1.57
Reinjection during procedure				
No. of subjects	2	4	18	16
Mean, mL	1.0	1.66	2.75 (n=17)	2.13 (n=15)
Mean waiting time, min	2.0 (n=11)	2.0 (n=7)	4.58	4.23
Quality of anesthesia rated very satisfactory, no. of subjects				
Start of procedure:				
Subject evaluation	47	43	42	45
Investigator evaluation	47	41	43	46
End of procedure:				
Subject evaluation	4 (n=5)*	6 (n=6)*	44 (n=47)	47 (n=48)
Investigator evaluation	4 (n=5)	6 (n=6)	45 (n=47)	47 (n=48)
Mean overall investigator evaluation (scale of 1 to 10)	9.88 (n=49)	9.89	8.73 (n=49)	9.62 (n=49)

In this table, "investigator" refers to the dental surgeon who administered anesthesia and performed the procedure.
n.r.= not reported
Not reported for remaining subjects
Extracted from Study Reports France A and France B, Section 8.4.3.

[taken from sponsor's table , Vol. 1.40, p. 41., and Vol. 1.39, pp.302, 364.]

"Both subject and investigator evaluation of quality of anesthesia at the start of the procedure was high for Septanest (84%-92% of patients rated anesthesia very satisfactory). The overall investigator score (based on effectiveness and tolerance) was virtually identical for the two anesthetics in France A (9.88vs 9.889), but somewhat lower for Septanest (8.73) than for Alphacaine N (9.62) in France B."

[Vol. 1.40, p.41, Vol. 1.39, 302, 364.]

SECTION 7.2.5 OTHER CLINICAL TRIALS

In addition to the pivotal and supporting trials there were another three controlled, four uncontrolled, and seven pharmacodynamic studies cited by the sponsor to support efficacy of Septanest.

The controlled studies were as follows:

Donaldson et al (1987) found no statistically significant differences between articaine HCl and prilocaine for onset time or duration of anesthesia for either infiltration or nerve block

Wright et al (1991) studying 75 children drew the following conclusions:

1. Little or no pain was experienced by 65% of subjects.
2. Children who demonstrate comfort at the time of injection are likely to exhibit no pain during successive procedures.
3. There is a high relationship between children behaving cooperatively and comfort during procedures.
4. When profoundness of anesthesia for all subjects was considered the three variables - tooth location, chronologic age and anesthetic type were not significant.

Hidding et al (1991), comparing articaine HCl, prilocaine, and lidocaine, observed very few differences with respect to effects on blood pressure, pulse rate and tissue rehabilitation. Most findings reflected differences that favored articaine with 1:100,00 epinephrine.

The uncontrolled studies were as follows:

Cowan (1977), in a review of the clinical data comparing local anesthetics, found that articaine with 5µg/mL epinephrine showed similar efficacy to lidocaine/epinephrine and mepivacaine/epinephrine preparations, and greater vasodilator properties than mepivacaine and prilocaine. Articaine with 5µg/mL showed reasonably rapid onset time with a satisfactory duration and extent for clinical purposes.

Dudkiewicz et al (1987), comparing articaine 1:100,000 epinephrine with articaine 1:200, 000 epinephrine in children ages 4 to 10, found anesthesia successful in all cases without reinjection. Latency was 10 to 15 minutes and duration was 120 minutes.

Lemay et al (1985) found articaine had a good efficacy profile with rapid action, deep anesthesia, sufficient total duration. and a rapid return of feeling using a small amount of anesthetic.

Rahn et al (1991) found the efficacy of 4% articaine 1:200,000 epinephrine was definitely more pronounced than 2% articaine without vasoconstrictor.

The pharmacodynamic studies were as follows:

Winther and Patirupanusara (1974) found that articaine HCl 3% + 5 µg/mL epinephrine had a significantly longer duration of analgesia than mepivacaine 3% + 5 µg /mL epinephrine but a shorter duration than articaine HCl 2% with 10 µg/mL epinephrine. Articaine HCl 3% and mepivacaine 3% without epinephrine did not provide adequate anesthesia.

Raab et al (1990) found that the time to onset was shorter for 4% articaine HCl/epinephrine solutions than for the 2% solutions. The 2% solutions also showed a higher degree of variability in duration than the 4% solutions.

Ruprecht and Knoll-Kohler (1991) reported that duration was statistically longer for articaine 4% compared to equimolar concentrations of lidocaine. The duration was not significantly altered by increasing the epinephrine from 1:200,000 to 1:100,000. No significant difference was noted between articaine 4% 1:100,000 epinephrine and articaine 2.4% 1:100,000 epinephrine. Also no difference was noted between articaine 4% 1:100,000 epinephrine and 4% articaine 1:200,000 epinephrine.

Vahatalo et al (1993) reported that articaine 4% 1:200,000 and lidocaine 2% 1:80,000 epinephrine produced adequate anesthesia. Articaine had a shorter onset and a longer duration but these results were not statistically significant.

Von Sitzmann and Lindorf (1976) studying 12 patients, found a shorter onset time and longer duration for articaine 4% 1:200,000 epinephrine in the upper jaw compared to lidocaine 2% 1:200,000 epinephrine. Articaine 4% produced complete tooth anesthesia in 90% of subjects compared to 80% for subjects receiving lidocaine. In the lower jaw, subjects who received articaine 4% 1:200,000 epinephrine showed 87% with complete tooth anesthesia. Subjects who received lidocaine 2% 1:200,000 epinephrine could not achieve successful anesthesia in the lower jaw.

Raab et al (1990) compared time to onset and duration in 4% articaine 1:200,000 epinephrine, mepivacaine 3% 1:25,000 norepinephrine, and Butanilicaine 3% without vasoconstrictor. For articaine HCl the time to onset was 3.8 ± 1.2 min., duration was 62 ± 28 min. For Mepivacaine the time to onset was 4.1 ± 1.8 min., the duration was 72 ± 24 min. There were no significant differences between articaine and Mepivacaine during the ebb period (time until the pain threshold returned to the baseline value). Butanilicaine without vasoconstrictor provided no adequate anesthesia. An adequate treatment duration of 6 minutes was seen in only one subject

Winther and Nathalang (1972) noted that articaine 2% and 4% both without epinephrine, did not provide effective anesthesia; however, when articaine HCl was administered with 5 µg/mL epinephrine, statistically significant longer durations were observed compared to controls. Also, duration of tooth analgesia increased with increasing articaine HCl concentration.

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