CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
20-971

Administrative Documents

14. PatentCertification

septodont

DEPROCO, Inc.

245-C Quigley Boulevard
New Castle
Delaware 19720
Phone: 302-328-1102
Fax: 302-328-5653

DECLARATION

In my capacity as President of DEPROCO INC., I declare, in accordance with the requirements of 21 C.F.R. par.314.53 (c)(3) that to the best of my knowledge and belief, no patents exist that claim articaine hydrochloride or epinephrine or the combination thereof, or that claim a method of using articaine hydrochloride in combination with epinephrine, and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of such a patent engaged in the manufacture, use or sale of articaine hydrochloride in combination with epinephrine.

January 14, 1998

DEPROCO INC.

David HALIMI
President

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	20971	**Trade Name:**	
Supplement Number:		**Generic Name:**	Articaine hydrochloride 4% Epinephrine 1:100,000
Supplement Type:		**Dosage Form:**	Injectable; Injection
Regulatory Action:	AP	**Proposed Indication:**	Indicated for local, infiltrative, or conductive anesthesia in both simple and complex dental and periodontal procedures.

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

YES, Pediatric data exists for at least one proposed indication which supports pediatric approval

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days)
____Infants (1-24 Months)
____Children (25 Months-12 years)
____Adolescents (13-16 Years)
X Other Age Groups (listed): 4 to 16 year olds

Label Adequacy	Adequate for SOME pediatric age groups
Formulation Status	NO NEW FORMULATION is needed
Studies Needed	No further STUDIES are needed
Study Status	

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:

Dental procedures are not customarily done with local anesthesia prior to age 4. The sponsor's pediatric evaluation is adequate.

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, LAURA GOVERNALE

Signature _____ Date 3-31-00

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA/PLA/PMA # 20-971 Supplement # 000 Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-170 Action: AE

Trade and generic names/dosage form: Septanest (Articaine Hydrochloride 4% with Epinephrine 1/200,000 solution for injection) and Septanest (Articaine Hydrochloride 4% with Epinephrine 1/100,000 solution for injection).

Applicant Deproco, Inc., Septodont Therapeutic Class 1S

Indication(s) previously approved NONE

Pediatric information in labeling of approved indication(s) is adequate ___ inadequate ___

Indication in this application for infiltration and nerve block anesthesia in general dentistry (For supplements, answer the following questions in relation to the proposed indication.)

X 1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all revelant pediatric age groups. Further information is not required. (Please see back.)

___ 2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

___ 3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

___ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

___ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

___ c. The applicant has committed to doing such studies as will be required.
___ (1) Studies are ongoing,
___ (2) Protocols were submitted and approved.
___ (3) Protocols were submitted and are under review.
___ (4) If no protocol has been submitted, attach memo describing status of discussions.

___ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

___ 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

___ 5. **If none of the above apply,** attach an explanation, as necessary.

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

S , MD 1/20/99

Signature of Preparer and Title Director DAAOADP Date

cc: Orig NDA 20-971
HFD-170/Div Files
NDA/PLA Action Package
HFD-006/ SOlmstead (plus, for CDER/CBER APs and AEs, copy of action letter and labeling)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action. (revised 1/19/99)

Attachment A

DEBARMENT CERTIFICATION STATEMENT

Deproco, Inc., hereby certifies that it did not and will not use, in any capacity, the services of any person debarred under Section 306 of the act in connection with this application.

APPEARS THIS WAY
ON ORIGINAL

Redacted 1

pages of trade

secret and/or

confidential

commercial

information

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS
HFD-170, Room 9B-45, 5600 Fishers Lane, Rockville MD 20857
Tel:(301) 827-7410

MEMORANDUM

DATE: April 3, 2000 /S/

FROM: Cynthia G. McCormick, MD, Director
Division of Anesthetic, Critical Care and Addiction Drug Products
Office of Drug Evaluation II, CDER, FDA

TO: Lisa Rarick, MD, Deputy Director
Office of Drug Evaluation II, CDER, FDA

File, NDA # 20-971 articaine HCl with 1:100,000 epinephrine

CC: John K. Jenkins, MD, Director
Office of Drug Evaluation II, CDER, FDA

RE: Recommended Action for NDA # 20-971, Septocaine (articaine HCl 4% with epinephrine 1:100,000 solution for injection)

Articaine HCl is an amide local anesthetic for dental procedures for which an NDA was submitted to the agency March 30, 1998. An Approvable letter (dated January 29, 1999) was sent to Deproco Inc, the US subsidiary for Spécialités Septodont, a French company, detailing the following deficiencies: need for an inspection, rejection of proposed nomenclature, issues surrounding the instability of epinephrine and requirements of allowable overage, and agreement on the final printed labeling. The basis for the approvability was the finding of safety and efficacy of articaine HCl drawn from clinical studies conducted with articaine HCl with 1:100,000 epinephrine. A complete response was received on May 4, 1999 and because of a failed manufacturing site inspection, a second approvable letter was sent. This submission received on February 3, 2000 represents the second complete response to the approvable letters. At the present time, there are two significant issues, neither specifically referenced in the approvable letter. One of these issues was detected upon review of the final labeling which failed to provide specific instructions for appropriate selection between the two formulations. This led to a final closer inspection of the now completed package. The second relates to

additional problems identified by OPDRA with the name of the product. These will be discussed further within this memo.

Nonclinical toxicology
The nonclinical studies were performed with the to-be-marketed U.S. formulation and with the marketed European formulation, which differs in the quantity of the preservative, sodium metabisulfite and presence of EDTA. The toxicity which was reported in these studies was not unexpected from this class of drugs, and the NOAEL for adverse events such as seizures and extramedullary hematopoesis occurred with a sufficient margin of safety so as not to be of concern in human administration[1]. As noted below, articaine given by local infiltration does not achieve significant plasma levels and in addition it is rapidly converted to the inactive metabolite, articainic acid. Reproductive toxicity studies were significant for maternal toxicity in high doses and minor cognitive abnormalities and minor skeletal abnormalities in offspring, in two species, possibly also related to maternal toxicity.

The nonclinical safety of the second active ingredient, epinephrine, was derived from the agency's prior finding of safety in previously approved lidocaine with epinephrine (the reference listed product for epinephrine), comparisons of the LD50s in rats and mice between articaine and articaine with epinephrine, reproductive toxicity and mutagenicity studies of articaine with epinephrine. Epinephrine administered in both proposed formulations does not achieve measurable plasma concentrations.

Carcinogenicity studies were not required, and would not normally be required for either active ingredient for a local anesthetic used on an occasional basis.

Safety and Efficacy—established previously
The basis for the finding of safety and efficacy for articaine HCl with epinephrine as a local anesthetic for dental procedures was described previously in the clinical review and in Dr. Rappaport's supervisory memo of January 13, 1999. These findings were the basis for the approvable letter of January 29, 1999. Articaine HCl was formulated with epinephrine in order to induce local vasoconstriction, which is expected to slow systemic absorption of articaine, and prolong tissue concentrations and thus, the duration of the effect. It is also expected to reduce systemic levels of articaine.

The efficacy of articaine HCl 4% with epinephrine 1:100,000 solution for injection has been adequately demonstrated for inducing local anesthesia in three randomized, double-blind, active-controlled trials (baseline control implied) in both simple and complex painful dental procedures using both formulations against lidocaine. In these studies no superiority to the active control, lidocaine, was demonstrated and none is claimed.

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[1] The comparisons between Cmax and AUCs for articaine and articainic acid following administration in humans with the NOEL in animals are found on page 30/36 of the Review of Nonclinical Data, Dr. Goheer.

There has been an adequate evaluation of the safety of articaine in over 1000 patients and subjects (all but 50 were given the US formulation) with only minor adverse events reported. The development program also included adequate numbers of children as young as 4 years of age. (Local anesthesia for children younger than 4 years is not a generally recommended practice for dental procedures). The number of pediatric patients in the 4-13 year age group prospectively studied in this NDA was limited. However reports using the European formulation[2] in 66 children from 4 to 6 years of age, confirmed the expected profile of few adverse events. The pharmacokinetics of articaine in the pediatric population, as noted by Dr.Doddapaneni, does not differ significantly from the adult, and contributes to the review team's assessment that the product should perform similarly in children, both in terms of efficacy and safety. There were no serious or life-threatening adverse events reported in this NDA.

There were two formulations in the NDA proposed for articaine: articaine HCl 4% (40 mg/mL) with epinephrine 1:100,000 solution for injection and a lower epinephrine content product, articaine HCl 4% (40 mg/mL) with epinephrine 1:200,000 solution for injection. Dr. Blatt states in his initial review of this NDA[3] dated October 2, 1998 that "the FDA agreed it was unnecessary to independently test 4% articaine hydrochloride with 1:200,000 epinephrine, or to test the efficacy of epinephrine." However, it appears, based on minutes generated by the sponsor[4], that the FDA stated that it was appropriate to study the formulation with the higher epinephrine concentration in clinical trials to generate the majority of safety data, but at that meeting there was also discussion about what would be needed in addition. Specifically, Dr. Fred Hyman noted that if the sponsor wanted to make labeling claims regarding quicker onset, deeper anesthesia, or shorter duration of anesthesia of one formulation, they would have to demonstrate these effects definitively. The sponsor did not go on to study these two formulations in head-to-head comparisons, thus, no comparative pharmacodynamic data were generated and clear differences between the two formulations have not been properly identified. Without such information it is not possible to develop adequate labeling to describe for the dental practitioner the circumstances under which one formulation should be used in preference to the other. While neither the FDA nor the sponsor fully anticipated this deficiency during the development of the product, and this deficiency was not identified in the original or subsequent NDA action letters, there appears to be no obvious basis upon which to approve the 4% articaine hydrochloride with 1:200,000 epinephrine formulation.

The sponsor was asked in teleconferences on March 16 and 30, 2000 to delineate the relevant clinical differences, based on data within the NDA, which would allow for meaningful product labeling of both formulations. Their response is carefully reflected in Dr. Blatt's amended review dated March 28, 2000 and in the following table are additional data from portions of the

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[2] The European formulation, as noted, differs only in amount of sodium metabisulfite and EDTA used as a preservative.

[3] Review of NDA 20-971 p.10

[4] Minutes of Meeting between FDA and Deproco, March 10, 1996

ISE and NDA referenced articles, highlighting the best case for a separation between the two formulations in head-to-head comparisons.

Onset and Duration of Anesthesia following Administration of Articaine 4% with Epinephrine (adults)

Formulation of epinephrine	Onset (minutes)	Mean Duration (minutes)	Route/dose	source
1:200,000	1.98 ± 1.4 (118.6 ± 83.6 sec)	Not provided	infiltration	Lemay et al, 1985 N=108
1:100,000	1.76± 0.82 (105±49.2 sec)	Not provided	infiltration	
1:200,000	2.83 ± 2.18 (170 ±130.5 sec)	Not provided	nerve block	
1:100,000	2.03±0.94 (122.1±56.4 sec)	Not provided	nerve block	
Articaine 4% w/ 1:200.000	4.7±1.58	54.4 ± 22.58	Vestibular infiltration 0.5 mL	Ruprect and Knoll-Kohler, 1991[5] N=10 for each arm
Articaine 4% w/ 1:100,000 epinephrine	5.0±2.83	66.8 ± 22.7	Vestibular infiltration 0.5 mL	Electrical stim of dental pulp
Articaine 4% w/ 1:200,000 epinephriine	1.8 ±1.2	56.7 ±24.2	Maxillary infiltration, 1.7 mL	Raab, et al 1995 N=26
Articaine 4% 1:100,000 epinephriine	2.8 ± 2.8	53.7 ±19.7	Maxillary infiltration, 1.7 mL	

It is clear from the table above that the site of infiltration or nerve block, and the dose used may play a role in the latency of effect and duration of anesthesia, but that there is no reproducible defining characteristic profile based on formulation as documented in the literature references provided that should allow distinction between these two formulations. A head-to-head comparison of similar infiltrative techniques and sites as well as doses could have been performed prospectively to provide the appropriate data to distinguish the profiles of the two formulations. As noted above the results from the literature were inconsistent and failed to distinguish between the formulations.

[5] The authors state "The anesthetic action times of the 125 mM (=4%) articaine HCl...were not altered significantly by increasing the epinephrine additive from 1:200,000 to 1:100,00."

In an effort to establish some other basis for approving the articaine HCl 4% with epinephrine 1:200,000 formulation, the review team studied approval documents for NDA 6-488 and subsequent supplements for lidocaine formulated with and without epinephrine (approved in 1948), the product after which all generic formulations were based. It was found that the lidocaine for local anesthesia in dentistry was approved in three formulations: lidocaine 2% without epinephrine, lidocaine 2% with 1:100,000 epinephrine, and lidocaine 2% with 1:50,000 epinephrine. There is no lidocaine with 1:200,000 epinephrine formulation approved for dental procedures. The labeling for this product states under dosage and administration:

> For most routine dental procedures, Xylocaine solution 2% with epinephrine 1:100,000 is preferred. However when a greater depth and more pronounced hemostasis are required, a 1:50,000-epinephrine concentration should be used.

There is a separate label for lidocaine (also NDA 6-488) with and without epinephrine approved as an anesthetic for infiltration and nerve block, which does include lidocaine (0.5%, 1%, 1.5% and 2%) with 1:200,000 epinephrine. However, none of these were approved for anesthesia in dentistry. It appears that if the lidocaine with 1:200,000 epinephrine is used in the dental setting as proposed by the sponsor, constitutes off-label use.

The sponsor's own approved lidocaine with epinephrine formulations for local anesthesia in dentistry (generic) also include only lidocaine 2% with 1:100,000 epinephrine, and lidocaine 1:50,000 epinephrine. There also appears to be no distinguishing PD profile between these two formulations, and no instructions in the package insert for use of one formulation in preference to the other.

In summary, articaine HCl 4% (40 mg/mL) with epinephrine 1:100,000 was studied in clinical trials which established the efficacy and safety of the combination product. Articaine HCl 4% (40 mg/mL) with epinephrine 1:200,000 was not, except in a single PK/PD trial. Based on the data submitted in the NDA there is no evidence that the two products differ in the latency of effect or duration of anesthesia or in any other way which would support a labeling claim. There is additionally, no prior finding by the Agency (no approved NDA or DESI finding) for other local anesthetics for dentistry formulated with epinephrine to support the approval of articaine HCl 4% (40 mg/mL) with epinephrine 1:200,000.

PDUFA provides for the issuance of action letters which approve human drug applications or which set forth in detail the specific deficiencies in such applications and, where appropriate, the actions necessary to place such applications in condition for approval. While the specific deficiency with regard to the 4% articaine hydrochloride with 1:200,000 epinephrine formulation was not identified in the original and subsequent approvable letters, the overall approvablility of articaine HCl was never in question, since the findings of safety and efficacy were provided. An approvable letter indicates that FDA is prepared to approve the application upon the satisfactory

resolution of conditions specified in the approvable letter. Among the deficiencies identified in the approvable letter was agreement on the final printed labeling. The difficulty with this application arises from the inability to craft appropriate labeling to incorporate directions for use of the 4% articaine hydrochloride with 1:200,000 epinephrine formulation. The proposed solution is the approval of the 4% articaine hydrochloride with 1:100,000-epinephrine formulation with directions for use. The sponsor understands that if marketing of the articaine HCl with epinephrine 1:200,000 formulation is desired, an efficacy supplement could be approved at a later date if, when the two products are studied in direct head-to-head comparison, a meaningful clinical difference is found providing a basis for selection between the two formulations.

Since the NDA was originally submitted there have been no additional clinical trials and therefore no new exposures to articaine. Postmarketing data were submitted with no significant signal identified.

Biopharmaceutics

The product, as expected for a local anesthetic agent, does not achieve significant plasma levels. It is rapidly absorbed and highly metabolized to articainic acid (inactive) and there have been no other toxic metabolites identified. The onset of action, based on PK studies (using 4% articaine with 1:200,000 epinephrine) is 3.65 ±minutes and has a duration of action of 68.2 ±8.3 minutes. Articaine has been extensively used in Canada and Europe and the pharmacokinetics evaluation of the drug have been summarized from previously performed studies on the French formulation, with a prospective bridging study to the US formulation.

The several requests identified in the biopharmaceutics review and evaluation of clinical data may be obtained post approval and do not involve the need of any information that would impact on the approvability of the product.

Regulatory

Not specifically addressed in the previous submission, the sponsor had initially submitted this application under 505(b)(1) of the Act. Upon careful examination of the nonclinical, clinical and biopharmaceutics data sources, it is clear that literature references and studies performed by another manufacturer have been relied upon for approval. The manufacturer of this product has conceded that they have no right of reference to the product for the studies, which they referenced. The sponsor has amended the application under 505(b)(2) to reflect this status. No reference listed products for articaine exist in the US market and there was, therefore, no requirement for a relative bioavailability study. The comparison to lidocaine HCl with 1:100,000 epinephrine was sufficient to satisfy the requirements for a relative bioavailability study for the epinephrine ingredient as discussed by Dr. Uppoor in her review. However, as pointed out earlier in this memo, there is no approved local anesthetic product for dentistry that is formulated with epinephrine 1:200,000.

Chemistry Manufacturing and Controls
The chemistry issues outlined during the review process have been largely resolved.

The first of these relates to the shelf life of the product given the instability of epinephrine. The sponsor had been given the previous advice that the product would be approved for a shelf life of one year due to the degradation of epinephrine. The Agency does not generally approve the addition of 15% overage of any active ingredient or excipient merely to extend the shelf life. However in the case of this epinephrine-containing product, due to the instability of epinephrine, and the Agency's acceptance of the 15% overage for other similar dental products in the generic drug setting, and due to the likely confusion that the exact labeling of this product would create, ONDC made the exception that a 15% overage should be approved in this case. This would include 7% to account for manufacturing loss as described in Dr. D Sa's memorandum and 10% post-manufacturing degradation.

new upgraded facility was not prepared for inspection during the first NDA cycle and therefore an inspection of the drug substance manufacturing facilities in France did not take place initially. Since the second approvable letter the inspections of drug substance and drug product manufacturing facilities have been completed and are acceptable.

Nomenclature
On the first cycle of review the Labeling and Nomenclature Committee rejected the name Septanest because the was thought to be misleading, indicating a higher strength. This is not the case, in fact the refers to a higher dose of epinephrine. The committee argued that if the company chose to submit a higher strength product in the future, the name would become even more confusing. The committee suggested that the concentration of epinephrine be added to the name. This was done.

Since that time a second evaluation of the name was undertaken by OPDRA. At this time the name Septanest was rejected because of the similarity to Citanest (prilocaine), also a dental anesthetic. Because articaine contains sodium metabisulfite and only one formulation of Citanest contains sodium metabisulfite, it was thought that this would potentially pose a serious risk to the sulfur-allergic patient if an error occurred in which Septanest was given instead of Citanest. In addition, for patients who might be allergic to either prilocaine or articaine, there is the potential risk of serious allergic reaction if the two products are confused. The company undertook to collect all reports of medication errors of accidental substitution of Citanest for Septanest and Septanest for Citanest in countries where both Citanest and Septanest are marketed under those trade names. The company was unable to obtain such reports of adverse events. An additional name Septocaine has been proposed by the sponsor and has been found acceptable by the Agency.

Labeling
It was required that the cartridge imprinting be improved to prevent rubbing off with normal use. The sponsor has improved the technique for labeling the cartridges.

The sponsor was required to print prominently on the cartridge and package that articaine contains sodium metabisulfite. This has been done.

Recommendation:
Approval of Septocaine (articaine HCl 4% with epinephrine 1/100,000 solution for injection) for infiltration and nerve block for dental procedures with the attached labeling.

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS

HFD-170, Room 9B-45, 5600 Fishers Lane, Rockville MD 20857
Tel:(301) 827-7410

MEMORANDUM

to: Victor Raczkowski, MD
Acting Director, ODE III

Division File: NDA # 20-971
DFS: NDA # 20-971 (N000)

from: Cynthia McCormick, MD /S/ MD
Director, Division of Anesthetics, Critical Care and Addiction Drug Products

subject: Septanest (articaine HCl 4% with epinephrine 1/200,000 solution for injection)
Septanest (articaine HCl 4% with epinephrine 1/100,000 solution for injection)
Approvable Action Memo

date: January 13, 1999

Dr. Rappaport has summarized the overall NDA for Septanest accurately and concisely and I agree with his conclusions. I will briefly recapitulate the basis for the Division's recommendation for approvability of this NDA.

As Dr.Rappaport has pointed out, there are two-formulations of articaine, an anesthetic agent evaluated for local dental anesthesia (infiltration and local nerve block): Septanest (articaine HCl 4% with epinephrine 1/200,000 solution for injection) and Septanest (articaine HCl 4% with epinephrine 1/100,000 solution for injection). Septanest is formulated with epinephrine in order to induce local vasoconstriction and delay the systemic absorption of the anesthetic agent. Septanest (articaine HCl 4% with epinephrine 1/100,000 solution for injection) contains a higer concentrtion of epinephrine which increases the duration of the effect and decreases systemic levels of articaine but is expected to have more associated adverse events.

The efficacy of this product has been adequately demonstrated in control of pain in double-blind, active-controlled trials (baseline control implied) using both formulations against lidocaine in painful dental procedures, both simple and complex. Dr. Blatt, the primary clinical reviewer for this product, describes these in detail. The three pivotal studies used the 4% articaine with higher

Requirements of Approval:

Resolution of the following CMC deficiencies should be required for approval

- Satisfactory approval of the manufacturing facilities
- Satisfactory resolution of the packaging deficiencies

Acceptance of the final printed labeling (attached) should also be a requirement of approval.

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS
HFD-170, Room 9B-45, 5600 Fishers Lane, Rockville MD 20857 Tel:(301)443-3741

MEMORANDUM

DATE: January 13, 1999

TO: File, NDA 20-971

FROM: Bob A. Rappaport, M.D.
Deputy Director, DACCADP

THROUGH: Cynthia G. McCormick, M.D. J. McCormick
Director, DACCADP
1/14/99

RE: Supervisory Review of NDA 20-971 Septanest (articaine hydrochloride 4% with epinephrine 1:200,000 or 1:100,000)

BACKGROUND:

NDA 20-971 for Septanest (articaine hydrochloride 4% with epinephrine 1:200,000 or 1:100,000, was submitted by Deproco Inc. on March 30, 1998. Articaine HCl was first synthesized in Europe in the 1960's. Spécialités Septodont manufactures articaine in France and has marketed under the name Septanest in various countries for several years. Deproco is the U.S. subsidiary of Spécialités Septodont. The original NDA for Septanest, [redacted] was submitted to the Agency on October 18, 1996. IND

This application contains complete reports for five clinical and twelve pharmacokinetic studies. The submission also contains a number of published articles relating to the efficacy and safety of articaine. The clinical studies of the effectiveness and safety of this new formulation, as well as the literature references, have been reviewed [submitted March 30, 1998] by Harold Blatt, DDS The application has also been reviewed by Chuanpu Hu, Ph.D. (biostatistics), Ramana Uppoor, Ph.D. (clinical pharmacology and biopharmaceutics), Anwar Goheer, Ph.D. (pharmacology/toxicology), Pramoda Maturu, Ph.D. (chemistry), and Michael Kline, Ph.D. (abuse liability). In this memo, I will briefly

review the effectiveness and safety data summarized in the primary clinical review, as well as any relevant information found in the primary reviews from the other disciplines, and make appropriate recommendations for action on the NDA.

EFFECTIVENESS:

Evidence of efficacy has been submitted in the clinical studies 96001.02UK, 96001.02US and 96002.01US, as well as three supportive studies.

Study 96001.02UK:

This was a randomized, double-blind, parallel, active-controlled, multicenter, single dose study comparing the effect of 4% articaine HCl with 1:100,000 epinephrine with 2% lidocaine HCl with 1:100,000 epinephrine administered parenterally in patients undergoing dental procedures. Most routine dental procedures were allowed.

The study consisted of a screening visit, a treatment visit, and two follow-up telephone calls. On the treatment day, patients were randomized 2:1, articaine:lidocaine, and treated with study drug shortly before undergoing the dental procedure. Study drug was used on an as needed basis, but was not to exceed a total dose of 7 mg/kg. Patients recorded their level of pain experienced during the procedure using a 10 cm VAS rated from "0 = no pain" to "10 = worst pain imaginable." A similar VAS will be used by the investigators to score their patients pain level. For children ages 4 through 12 years, a VAS with 'smiley faces' was used. Follow-up phone calls to assess adverse events were made within the first 24 hours after discharge from the study center and 7 days after treatment.

The primary efficacy variable is the level of pain experienced during the dental procedure as measured on the VAS by both patient and investigator. Patients were to be stratified by simple (single extractions with no complications, routine operative procedures, single apical resections, and single crown procedures) vs. complex procedure (multiple extractions, multiple crowns and/or bridge procedures, multiple apical resections, alveolectomies, muco-gingival operations, and other surgical procedures of the bone).

Results:

The following table, based on Dr. Blatt's table on page 17 of his review, summarizes the patient disposition in this study:

Table 1.

	4% articaine	2% lidocaine	Total
All randomized patients	159	84	243
Randomized, not treated	1*	0	1
All treated patients	158	84	242
Completed study	139 (88%)	69 (82%)	208 (86%)
Discontinued patients:			
Protocol deviation	17 (11%)	12 (14%)	29 (12%)
Lost to follow-up	1 (1%)	3 (4%)	4 (2%)
Other	1 (1%)	0	1 (<1%)

* patient took NSAID within 24 hours of study

Treatment groups appeared to be generally matched on relevant measures at baseline.

Primary Efficacy Analyses:

The VAS scores are summarized in the following copy of Dr. Blatt's table found on page 21 of his review:

Table 2.

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				

No statistically significant difference was found between the treatment groups ($p > 0.5$).

Study 96001.02US:

This was a randomized, double-blind, parallel, active-controlled, multicenter, single dose study comparing the effect of 4% articaine HCl with 1:100,000 epinephrine with 2% lidocaine HCl with 1:100,000 epinephrine administered parenterally in patients undergoing dental procedures. Most routine dental procedures were allowed.

The study consisted of a screening visit, a treatment visit, and two follow-up telephone calls. On the treatment day, patients were randomized 2:1, articaine:lidocaine, and

treated with study drug shortly before undergoing the dental procedure. Study drug was used on an as needed basis, but was not to exceed a total dose of 7 mg/kg. Patients recorded their level of pain experienced during the procedure using a 10 cm VAS rated from "0 = no pain" to "10 = worst pain imaginable." A similar VAS will be used by the investigators to score their patients pain level. For children ages 4 through 12 years, a VAS with 'smiley faces' was used. Follow-up phone calls to assess adverse events were made within the first 24 hours after discharge from the study center and 7 days after treatment.

The primary efficacy variable is the level of pain experienced during the dental procedure as measured on the VAS by both patient and investigator. Patients were to be stratified by simple (single extractions with no complications, routine operative procedures, single apical resections, and single crown procedures) vs. complex procedure (multiple extractions, multiple crowns and/or bridge procedures, multiple apical resections, alveolectomies, muco-gingival operations, and other surgical procedures of the bone).

Results:

The following table, based on Dr. Blatt's table on page 29 of his review, summarizes the patient disposition in this study:

Table 3.

	4% articaine	2% lidocaine	Total
All randomized patients	569	284	853
All treated patients	569	284	853
Completed study	568 (>99%)	283(>99%)	851 (>99%)
Discontinued patients:			
Adverse event	0	1 (<1%)	1 (<1%)
Protocol deviation	1 (<1%)	0	1 (<1%)

Treatment groups appeared to be generally matched on relevant measures at baseline.

Primary Efficacy Analyses:

The VAS scores are summarized in the following copy of Dr. Blatt's table found on page 32 of his review:

Table 4.

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				

No statistically significant difference was found between the treatment groups ($p > 0.5$).

Study 96002.01US:

This was a randomized, double-blind, parallel, active-controlled, multicenter, single dose study comparing the effect of 4% articaine HCl with 1:100,000 epinephrine with 2% lidocaine HCl with 1:100,000 epinephrine administered parenterally in patients undergoing dental procedures. Most routine dental procedures were allowed.

The study consisted of a screening visit, a treatment visit, and two follow-up telephone calls. On the treatment day, patients were randomized 2:1, articaine:lidocaine, and treated with study drug shortly before undergoing the dental procedure. Study drug was used on an as needed basis, but was not to exceed a total dose of 7 mg/kg. Patients

recorded their level of pain experienced during the procedure using a 10 cm VAS rated from "0 = no pain" to "10 = worst pain imaginable." A similar VAS will be used by the investigators to score their patients pain level. For children ages 4 through 12 years, a VAS with 'smiley faces' was used. Follow-up phone calls to assess adverse events were made within the first 24 hours after discharge from the study center and 7 days after treatment.

The primary efficacy variable is the level of pain experienced during the dental procedure as measured on the VAS by both patient and investigator. Patients were to be stratified by simple (single extractions with no complications, routine operative procedures, single apical resections, and single crown procedures) vs. complex procedure (multiple extractions, multiple crowns and/or bridge procedures, multiple apical resections, alveolectomies, muco-gingival operations, and other surgical procedures of the bone).

Results:

The following table, based on Dr. Blatt's table on page 17 of his review, summarizes the patient disposition in this study:

Table 5.

	4% articaine	2% lidocaine	Total
All randomized patients	155	75	230
All treated patients	155	75	230
Completed study	155 (100%)	73 (97%)	228 (99%)
Discontinued patients:			
Protocol deviation	13 (8%)	6 (8%)	19 (8%)
Lost to follow-up	0	2 (3%)	2 (1%)

Treatment groups appeared to be generally matched on relevant measures at baseline.

Primary Efficacy Analyses:

The VAS scores are summarized in the following copy of Dr. Blatt's table found on page 41 of his review:

Table 6.

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				

No statistically significant difference was found between the treatment groups ($p > 0.5$).

Supportive Studies:

Two studies performed in France (A and B) used a slightly different formulation of the drug product which contained sodium edetate and had a higher concentration of sodium metabisulfite. In addition, the France B formulation contained epinephrine 1:200,000. These studies compared the Septanest SP and N formulations of articaine to the Alphacaine SP and N formulations of articaine [SP now called 1:100,000 and N called

1:200,000]. These studies enrolled approximately 50 patients per study arm. Results of these two studies are summarized in the following Table copied from Dr. Blatt's table on page 45 of his review.

Table 7.

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

	France A		France B	
	Septanest SP 4% articaine HCl with 1:100,000 epinephrine	Alphacaine SP 4% articaine HCl with 1:100,000 epinephrine	Septanest N 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.

A third study submitted in support of the sponsor's claim of effectiveness was Study S97001. This was an open label, non-randomized, pharmacokinetic/pharmacodynamic study in 20 healthy volunteers. It evaluated the efficacy of 4% articaine HCl 1:200,000

epinephrine, single dose (1.7 mL) and multiple dose (5.1 mL). Dr. Blatt's review of this study is based on a summary provided by the sponsor to the clinical portion of the NDA. A more detailed review of the study has been included in Dr. Uppoor's biopharmaceutics review. The only evidence of effectiveness that can be gleaned from this study is that the drug appeared to induce analgesia. However, it is not possible to determine the extent of placebo effect accounting for this analgesia to the stimulus, a low grade electrical current.

SAFETY:

A total of 983 patients and 20 healthy subjects received articaine in the sponsor's clinical program. Fifty-one of the 983 patients were exposed to the French formulation in the France A study. Fifty of the 983 patients were exposed to the French formulation with the 1:200,000 epinephrine dosage in the France B study. The 20 healthy subjects received the U.S./U.K. formulation in the PK study, but with epinephrine at 1:200,000. Exposure in the three pivotal trials is summarized in Dr. Blatt's table, copied from his review, page 50:

Table 8.

Study Drug Administration, Protocols S96001.02, S96002.01, and S96001.02UK

	Septanest® — (4% — Articaine HCl with 1:100,000 Epinephrine)		2% Lidocaine HCl with 1:100,000 Epinephrine	
	Simple	Complex	Simple	Complex
Number of Subjects	675	207	338	104*
Mean Volume ± SEM (mL)	2.5±0.0.7	4.2±0.15	2.6±0.09	4.5±0.21
Mean Dose ± SEM (mg/kg)	1.48±0.042	2.36±0.094	0.80±0.031	1.26±0.065

*Missing data for one patient.
Extracted from Table 2.1.1, Section 7.17.
[Item 7.4.2, Vol. 1.40, p.102]

Children under 13 years of age and under received approximately two-thirds the volume of articaine or lidocaine. Four patients received more than the recommended dose of 7 mg/kg. No adverse events were reported for these four patients who received dosages as high as 8.5 mg/kg.

Deaths:

There were no deaths reported in any of the studies included in this application.

Discontinuations:

No articaine treated patients were discontinued from the three pivotal trials or the supportive trials due to an adverse event.

Serious Adverse Events:

One serious adverse event was reported for a patient treated with articaine in Study S96001.02 UK. A 45 year old man was found to have a squamous cell carcinoma on his tongue which had been present for over one year prior to treatment. The lesion was excised and the patient is being followed. This event is clearly not related to the study drug. No other serious adverse events were reported from the pivotal or supportive studies.

Other Adverse Events:

In three pivotal efficacy studies, 22% of the articaine treated patients and 20% of the lidocaine treated patients experienced at least one adverse event. Four percent of patients in each group experienced adverse events believed to be related to study drug. All adverse events were mild to moderate in intensity with the exception of one case of infection and one of mouth ulceration, both cases occurring in articaine treated patients.

The following table (prepared by Dr. Blatt) summarizes the adverse events that occurred with an incidence of 1% or greater in articaine treated patients across the three pivotal studies:

Table 9.

Adverse Events in Controlled Trials with an Incidence Of 1% Or Greater in the Articaine Population

	4% Articaine HCl/1:100,000 Epinephrine		2% Lidocaine HCl/1:100,000 Epinephrine	
Body System COSTART Term	Patients N (%)	Events N	Patients N (%)	Events N
Number of Patients	882 (100%)		443 (100%)	
Body As A Whole				
Headache	31 (4%)	34	15 (3%)	17
Infection	10 (1%)	10	3 (<1%)	3
Pain	114 (13%)	120	54 (12%)	55
Digestive System				
Gingivitis	13 (1%)	14	5 (1%)	5
Nervous System				
Paresthesia	11 (1%)	11	2 (<1%)	2

The most common adverse events related to study medication for the articaine treated patients were: Paresthesia, hypesthesia, headache, infection, and pain. The percent occurrence was less than one in all cases.

Table 10.

	4% articaine /1:100,000 epinephrine	4% lidocaine/1:100,000 epinephrine
Paresthesia	0.90%	0.22%
Hypesthesia	0.68%	0.11%
Headache	0.56%	0.34%
Infection	0.45%	0.11%
Pain	0.34%	0

While headaches occurred in 4% of Septanest and Alphacaine treated patients, the most common adverse event reported in the France A and B studies was "pain at extraction site."

Table 11.

Pain at extraction site:	**Study A**		**Study B**	
	Septanest 1:100,000 epinephrine N (%)	Alphacaine SP 1:100,000 epinephrine N (%)	Septanest 1:200,000 epinephrine N (%)	Alphacaine N 1:200,000 epinephrine N (%)
After several hours	34 (67)	38 (78)	2 (4)	7 (14)
After 24 hours	26 (51)	24 (49)	8 (16)	9 (18)
After several days	9 (18)	11 (22)	42 (84)	39 (78)

[based on Dr. Blatt's table, page 53 of his review]

In the uncontrolled PK study, 15% (3/20) of subjects reported dizziness. All adverse events were considered mild and not drug related.

Both Drs. Blatt and Hu discuss the adverse event 'Paresthesia' at length in their reviews. A high incidence of paresthesias was previously reported with a foreign sponsor's marketed drug product. However, that product consisted of a different formulation; specifically it contained EDTA. The incidence of paresthesias in the three controlled trials reported on in this application is not statistically significantly higher in the articaine treated patients compared to the lidocaine treated patients. In addition, all cases resolved. Similarly, I disagree with Drs. Blatt and Hu in their assessment that nausea appeared to occur with greater frequency in the articaine treated patients. Again, there was no statistically significant difference between the treatment groups, and the incidence was <1% in both groups.

Vital Signs:

There were no clinically significant changes in vital signs in any of the studies.

CMC:

There are three matters which continue to be potential reasons for non-approval for this product.

1. The CMC inspection for the drug product has not been completed. The manufacturer and DMF holder, [redacted], has been unable to allow the inspection due to construction in the facility in question. They have recently indicated that the facility will be available for inspection in late February 1999.

2. The sponsor has requested a [redacted]% overage of the epinephrine component of the formulation to cover degradation post-manufacturing. This is unacceptable according to ONDC policy. The sponsor has been informed of this matter but has not responded to the information as of this date.

3. The written material on the ampoules provided to the Division is not legible, even immediately upon removing them from the outer packaging. We have asked the sponsor whether these ampoules are the same as the to-be-marketed product. We have not received a clear response as of this date.

COMMENTS:

The sponsor has submitted the results of two adequate and well-controlled clinical trials. Based on these results, Septanest appears to be safe and effective for controlling post-operative dental pain. This effectiveness appears to be similar or comparable to that lidocaine. Although the safety data base for the formulation which includes 1:200,000 epinephrine is small, there are no indications of increased toxicity, and the PK studies were performed with this formulation which should, as Dr. Uppoor notes in her review [p. 6], provide the most information regarding systemic toxicity.

A number of outstanding CMC matters exist which do not allow for immediate approval of this application.

RECOMMENDATIONS:

This sponsor should be informed that the application is approveable and that final approval will be obtained once adequate documentation that [redacted] has passed inspection, that Spécialités Septodont does not plan to include the [redacted]% epinephrine overage in their formulation, and that the ampoules which will be marketed will not have a problem with labeling legibility. The sponsor must also agree to the attached product labeling.

/S/

Bob A. Rappaport, M.D.

January 13, 1999

January 13, 1999

Cc: Original NDA 20-971
HFD-170: Division File
HFD-170:
McCormick
Rappaport
Blatt
Permutt
Uppoor
Jean
Goheer
D'Sa
Maturu
Nolan

HFD-705:
Hu

MEMORANDUM

Date: March 2, 2000 /S/ 3/13/00

From: Albinus D'Sa, Ph.D.
Chemistry Team Leader

To: Memo to the record for NDA 20-971, Septanest (Articaine HCl with 4% epinephrine 1:100,000 and 1:200,000 injection)

The purpose of this memo is to address the CMC issues involved in the approval process of the NDA and to provide a recommendation to the ORM division to decide on the approvability of the NDA.

Reference is made to CMC Team Leaders Memo dated May 6, 1999 and the Agency's letter dated May 7, 1999.

These are the outstanding issues that are currently pending:

1) The Package Insert (PI) should be modified to clearly indicate in the "Description" section and the "How Supplied" section that the product contains a 15% overage of epinephrine so that analysis of the product will accurately represent the drug formulation. The following statement should be added: " The product is formulated with a 15% overage of epinephrine".

2) The Cartridge Container label requires the phrase " Contains sodium metabisulphate" and the storage statement needs to change to "store at 25 °C (77 °F) with excursions permitted between 15 °C and 30 °C (59 °F and 86 °F).

3) The applicant has changed the imprinting on the label, from a —— printed label to an —— imprinting label. The change was instituted at the request of the agency, when the reviewer noticed that the label could easily rubbed off. In order to ensure that the proposed —— printed label stays in place the applicant should be asked to provide a test method and results that ascertain that the label does not rub off.

A summary of the issues that were resolved are as follows:

4) There was a problem with the inspections of drug product manufacturing facility, but this issue has now been resolved. The drug product manufacturing facility, Specialities Septodont, located at Maur de Fosses, Paris, France, have been adequately addressed. The Office of Compliance has determined that all manufacturing and testing facilities are now acceptable.

5) The overage issue was reconsidered and decided by the Office of Pharmaceutical Science (OPS) permitting the 15% overage for epinephrine based on the following facts (see attached OPS meeting minutes dated August 30, 1999, and telecon with the applicant dated October 30, 1999) :

- The drug product is formulated with a 15% overage of epinephrine. The product is formulated at 5.75 ug/mL instead of — ug/mL and 11.5 ug/mL instead of —— ug/mL. A— % loss has been demonstrated during the manufacturing process. Therefore the effective overage is —%, which amounts to — ug/mL and — ug/mL for the two strengths of epinephrine in the drug product.

- The US formulation marketed by the applicant differs from that approved in Europe. The marketed European formulation contains EDTA and is packaged in a carpule with a ——— stopper. The formulation to be marketed in the US does not contain EDTA and is packaged in a carpule with ——— stopper. The absence of EDTA adds to the instability of epinephrine. However, EDTA is known to increase the incidence of paresthesia, so it absence increases the safety of the product. The European formulation and the clinical material used in the US trials for this NDA were both formulated with a 15% overage.

- Finally, if the product were labeled as currently formulated and if the overage were not approved, it would be confusing to the dentist community. Instead of 1:100,000 and 1:200,000 epinephrine concentration, which is the normal representation of all dental anesthetics, if the product were to be labeled exactly as formulated, then the label would read as 1.15:100000, and 1.15:200,000 epinephrine concentration.

- The agency learned through the inspection of the Septodont facility that other epinephrine containing dental anesthetic products were marketed in the US as generic drugs with a 10-15% overage of epinephrine.

6) A note of clarification is provided that drug substance, aritcaine hydrochloride which is racemic mixture, is not tested by the drug substance (DS) manufacturer ——— or enantiomeric excess. However, the drug product manufacturer accepts the DS based on a zero optical rotation for a 4% aqueous solution, which is acceptable.

In conclusion, besides items #3, 4 and #5, all pending CMC issues have been adequately addressed and therefore from the CMC stand point this application is recommended for approval.

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

REQUEST FOR CONSULTATION

TO *(Division/Office)*: Mathew Thomas, M.D. HFD-Division of Scientific Investigation			FROM: HFD-170 (Division of Anesthetic, Critical Care, and Addiction Drug Products) Hal Blatt, Medical Officer	
DATE: June 12, 1998	IND NO.:	NDA NO.: 20-971	TYPE OF DOCUMENT :	DATE OF DOCUMENT: March 30, 1998
NAME OF DRUG: Septanest (Articaine)	PRIORITY CONSIDERATION: S		CLASSIFICATION OF DRUG: 1S	DESIRED COMPLETION DATE: August 14, 1998

NAME OF FIRM: Deproco Inc.

REASON FOR REQUEST

I. GENERAL

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

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER:	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER:

III. BIOPHARMACEUTICS

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

IV. DRUG EXPERIENCE

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

V. SCIENTIFIC INVESTIGATIONS

X CLINICAL	☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: Please conduct DSI investigations on applicable NDA 20-971 pivotal trials identified on Attachment 1. Final review due August 14, 1998.

Ken Nolan Project Manager, HFD-170 (3-3741) Pklwn 9B-45

c: Original NDA 20-971
HFD-170/Div. Files
HFD-170/McCormick/Rappaport/Blatt

SIGNATURE OF REQUESTER: /S/	METHOD OF DELIVERY (Check one): ☒MAIL ☐ HAND
SIGNATURE OF RECEIVER:	SIGNATURE OF DELIVERER:

Printed by Harold Blatt

Electronic Mail Message

Date: 07-Apr-1998 03:19pm
From: Kenneth Nolan
NOLANK
Dept: HFD-170 PKLN 9B45
Tel No: 301-443-3741 FAX 301-443-7068

ect: FWD: IND ——— (Deproco) Articaine

Mathew:

As requested, the sponsor states the pivotal studies include the following studies. Also the sponsor clarified the indication is For infiltration or nerve block anesthesia for dentistry. The study sites location information is forthcoming, upon receipt I will promptly forward.

Please note, the medical reviewer has not confirmed this information. I will attempt to get a confirmation of the pivotal stuies from the medical reviewer and forward.

Should you have questions regarding this matter, please let me know.

Thanks,

Ken

S96001.02 US - Phase III Study - 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

S-96002.01 - Phase III Study - A Single Dose Study to Evaluate 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

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

REQUEST FOR CONSULTATION

TO *(Division/Office)*: Peter Cooney, Ph.D., HFD-160

FROM: HFD-170 (Division of Anesthetic, Critical Care, and Addiction Drug Products) Pat Maturu Reviewing Chemist

June 12, 1998	IND NO.:	NDA NO.: 20-971	TYPE OF DOCUMENT: VOLUME 1.6 (or Vol 6 of 64)	DATE OF DOCUMENT: March 30, 1998

NAME OF DRUG: Septanest (Articaine)	PRIORITY CONSIDERATION: S	CLASSIFICATION OF DRUG: 1S	DESIRED COMPLETION DATE: August 14, 1998

NAME OF FIRM: Deproco Inc.

REASON FOR REQUEST

I. GENERAL

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

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW	☐ CHEMISTRY REVIEW
☐ END OF PHASE II MEETING	☐ PHARMACOLOGY
☐ CONTROLLED STUDIES	☐ BIOPHARMACEUTICS
☐ PROTOCOL REVIEW	☐ OTHER:
☐ OTHER:	

III. BIOPHARMACEUTICS

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

IV. DRUG EXPERIENCE

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

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: Please review NDA 20-971 Volume 1.6 (Volume 6 of 64) microbiology data. Final review due Friday, August 14, 1998.

CENTER FOR ... JUN 16 1998 HFD-160 EVALUATION AND RESEARCH

Ken Nolan Project Manager, HFD-170 (3-3741) Pklwn 9B-45

c: Original NDA 20-971
HFD-170/Div. Files
HFD-170/Maturu/D'Sa

SIGNATURE OF REQUESTER: 6-15-98

METHOD OF DELIVERY (Check one): ☐ MAIL ☒ HAND

SIGNATURE OF R... 6/15/98

SIGNATURE OF DELIVERER:

6/15/98

REQUEST FOR TRADEMARK REVIEW

To: Labeling and Nomenclature Committee
Attention: Dan Boring, Chair (HFD-530), 9201 Corporate Blvd, Room N461

From: Division of	HFD-
Attention: Dr. Dan Boring	Phone: 443-3741
Date: June 15, 1998	
Subject: Request for Assessment of a Trademark for a Proposed New Drug Product	
Proposed Trademark: Septanest	NDA/ANDA# 20-971
Established name, including dosage form: Articane Hydochloride 4% with Epinephrine 1/100,000 and 1/200,000	
Other trademarks by the same firm for companion products:	
Indications for Use (may be a summary if proposed statement is lengthy): Septanest is indicated for infiltration or nerve block anethesia for dentistry.	
Initial Comments from the submitter (concerns, observations, etc.): The sponsor states the N and SP acronyms denote the tradenames used for the European drug product(N-Normale and SP-Specialites). The acronyms also differentiate the 1/100,000 and 1/200,000 concentrations.	

Note: Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

Rev. December 95

CDER LABELING AND NOMENCLATURE COMMITTEE

CONSULT # 1034b	HFD# 530	PROPOSED PROPRIETARY NAME:	PROPOSED ESTABLISHED NAME:
ATTENTION: ABI D'SA		SEPTANEST	Articane Hydochloride 4% with Epinephrine 1/200,000

A. Look-alike/Sound-alike

	Potential for confusion:
CITANEST	___ Low XXX Medium XXX High
CITANEST FORTE	XXX Low ___ Medium ___ High
DURANEST	XXX Low ___ Medium ___ High
SEPTRA DS	___ Low XXX Medium ___ High
	___ Low ___ Medium ___ High

B. Misleading Aspects:

"SP" MEANS "SPINAL" IN THE UNITED STATES.

C. Other Concerns:

JUST USE THE EPINEPHRINE DOSAGE STRENGTH INSTEAD OF USING THE — HIGHLIGHT THE CONCENTRATION.

D. Established Name

XXX Satisfactory

___ Unsatisfactory/Reason

Recommended Established Name

E. Proprietary Name Recommendations:

XXX ACCEPTABLE ___ UNACCEPTABLE

USE A DIFFERENT MODIFIER INSTEAD OF THE —

F. Signature of Chair/Date /S/ 9/3/98

Ken: please note and inform the team and then the applicant that LNC has raised concerns about — following the Septanest

MEMORANDUM OF TELECON

DATE: April 3, 2000 TIME: 10:30 – 11:00 a.m.

APPLICATION NUMBER: NDA 20-971

BETWEEN:

Name: Wayne Matelski
Phone: 202-857-6340
Representing: Deproco, Inc.

AND

Name: Bob Rappaport, M.D., Deputy Director
Laura Governale, Pharm.D., Regulatory Project Manager
Division of Anesthetic, Critical Care, and Addiction Drug Products
HFD-170

SUBJECT: carton/cartridge labeling

During a brief teleconference between Mr. Matelski of Arent Fox and Dr. Rappaport and Laura Governale of FDA, a decision was made that the sponsor may be waived from the requirement to include the phrase [redacted]' on the cartridge labels. Also, it was agreed that the established name will be printed below the trade name within the same background for the immediate container and carton labels at the next printing.

/S/

Laura Governale, Pharm.D.
Regulatory Project Manager

TELECONFERENCE MINUTES

Meeting Date: March 16, 2000 **Time:** 2:00 – 2:30 pm
Location: 9B45 Conference Room
NDA: 20-971
Drug: Septanest® 1:100,000
Sponsor: Deproco, Inc.
Indication: Infiltration or nerve block anesthesia for dentistry
Type of Meeting: Type C Teleconference
Meeting Chair: Cynthia McCormick, M.D., Director
Minutes Recorder: Laura Governale, Pharm.D., Regulatory Project Manager

MAR 2 0 2000

FDA Attendees:	Titles:	Offices:
Cynthia McCormick, M.D.	Director	HFD-170
Bob Rappaport, M.D.	Deputy Director	HFD-170
Harold Blatt, M.D.	Medical Reviewer	HFD-170
Laura Governale, Pharm. D.	Regulatory Project Manager	HFD-170

Participants:	Titles:
Wayne Matelski, Esq.	
Brain Waldman	

Meeting Objective: The purpose of this teleconference was to relay labeling changes and present additional requests for information to the sponsor regarding this NDA.

General Discussion: Following introductions, Dr. McCormick presented the issues surrounding this NDA to the sponsor. The review team has made some changes to the package insert labeling. In addition, the Agency would like the sponsor to submit a justification for the formulation containing epinephrine concentration 1:200,000. After re-reviewing the studies that were submitted with the original submission, the Agency questions the need for this strength. All the clinical data were based on epinephrine strength 1: 100,000. The sponsor was instructed to submit their case for 1:200,000 strength of epinephrine. The Agency requires more than a theoretical reason to approve this strength; therefore, data from this submission should be referenced in the argument.

In terms of labeling, the Agency is moving away from percentage designation to mg/mL for indicating product strength. Mr. Matelski stated that the change would not be a problem for the package insert; however, there may not be enough room on the cartridge for the mg/mL designation. He will check into this.

Dr. McCormick relayed additional labeling changes to the sponsor. The label has been modified to include a statement of 15% epinephrine overage, and some editorial changes in the PK section. The Clinical Trials section of the label has undergone greater changes. The comparative claim with active control has been taken out since a superiority claim cannot be made in the label. "Septanest" has been replaced with "Trade Name" throughout the label pending resolution of the trade name issue. The remainder of the changes were minor and editorial in nature. The Agency will fax a copy of the revised label to the sponsor.

Mr. Matelski presented a status report on the trade name issue. A preliminary response to the questions raised in the March 8, 2000, teleconference will be submitted to the Agency later today. A complete response is not included because the data are still being compiled. After conversing with representatives in other countries marketing both Citanest® and Septanest®, no confusion reports have been identified thus far. France has not received such reports and neither have UK and Canada. A full response should be expected by next Tuesday, March 21, 2000.

Dr. McCormick inquired whether the sponsor intended not to change the trade name. Mr. Matelski replied that he hopes to justify that Septanest®, the current trade name, is a valid name. Mr. Matelski further added that the current name, Septanest® is used throughout the world and Astra, the marketer of Citanest® has not filed any trademark issues. Furthermore, the sulfite allergy concern may be greater between Citanest® Plain and Citanest® Forte, since the latter formulation contains sulfites. There is a greater potential for confusion within the same drug family name than between Citanest® and Septanest®. In addition, dentists generally use only one dental anesthetic in the office; therefore, the potential for confusion between these two trade names is lessened. Dr. Blatt was not in agreement that this is a routine practice.

Dr. Blatt commented that in his experience, dentists typically use 2-3 different dental anesthetics in practice. Mr. Matelski added this is not the main argument for the trade name issue and that more data will be sent to support the trade name Septanest®. From what has been gathered so far, Septanest® is a safer product than Citanest®.

Dr. McCormick agreed that the occurrence of methemoglobinemia is more an issue with Citanest® than Septanest®. However, reducing the potential name confusion by changing the trade name would be a better assurance of preventing this ADR.

Mr. Matelski closed this issue by offering to submit information in support of the trade name, Septanest®. The submission being put together for today will contain a revised FDA Form 356h as a 505(b)2 application and a response to sulfite warning labels on cartridges and cans. Color copies of the cans and boxes will be submitted at a later date. Furthermore, this submission will include cartridges of other products as an example of the imprinting process that will be used for Septanest®.

Dr. McCormick reiterated that the Agency is requesting foreign ADR data for Citanest® and Septanest® only. In addition, if no justification for epinephrine strength 1:200,000 can be found, the Agency may approve only the one strength, 1:100,000.

Dr. McCormick adjourned the teleconference.

Action Items:

- The Agency will provide the sponsor with a copy of the official meeting minutes.
- The Agency will fax a copy of the labeling changes to the sponsor.
- The sponsor will submit additional data in support of the current trade name, Septanest.
- The sponsor will include in today's submission sample cartridges as an example of the imprinting process, revised Form FDA 356h, and wording for sodium metabisulfite warnings.

Minutes prepared by: Laura Governale, Pharm.D.

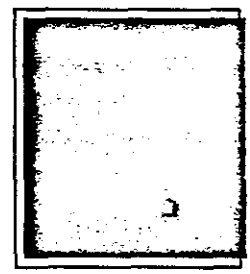
/S/ 3-20-00

Minutes concurred by Chair: Cynthia McCormick, M.D., Director

/S/

Printed from DFS

TELECON WITH SPONSOR MINUTES



Meeting Date: May 5, 1999 **Time**: 11:30 A.M.-12:00 Noon
Location: Parklawn Building 9B-45 **Sponsor:** Deproco, Inc.
NDA Name: 20-971, Septanest (Articaine Hydrochloride 4% with Epinephrine 1/100, 000 and 1/200,000)
Type of Meeting: To discuss the results of the review of sponsor's response to the approvable letter
Meeting Chair: Cynthia G. McCormick, M.D.
External Participant Lead: Wayne H. Matelski
Minutes Recorder: Susmita Samanta/ Project Manager

FDA Participants:	**Titles:**	**Offices:**
Cynthia G. McCormick, M.D.	Division Director	HFD-170
Bob Rappaport, M.D.	Deputy Division Director	HFD-170
Albinus D'Sa, Ph.D.	Team Leader/Chemistry	HFD-170
John Gibbs, Ph.D.	Supervisory Chemist	HFD-820
Steve Koepke	Supervisory Chemist	HFD-820
Pat Maturu, Ph.D.	Chemistry Reviewer	HFD-170
Corinne P. Moody	Chief, Project Management Staff	HFD-170
Susmita Samanta	Project Manager	HFD-170
Hal Blatt, D.D.S.	Medical Reviewer	HFD-170

Deproco Participants:	**Titles:**
Wayne H. Matelski	U.S. Agent for and Counsel to Deproco, Inc.

Meeting Objective:
The primary objective of this meeting was to discuss issues that are still pending for an approval and apprise the sponsor of the upcoming action.

Background:
An approvable action was taken on this application on January 29, 1999. The sponsor submitted a complete response on March 9, 1999, which was received by the division on the same day. After review, four concerns were raised: 1) The imprinting on the container is not acceptable 2) The name is not acceptable 3) Based on the stability data, only [redacted] month expiration can be granted, and 4) minor labeling changes are needed. Also, inspection of a facility is not acceptable.

Discussion:

Dr. McCormick led the discussion and informed the sponsor that they have satisfactorily resolved a number of issues, however, the following issues need to be resolved before approval:

- The FDA inspection of the drug product manufacturing facility, Specialites Septodont, revealed that the performance of the facility is unacceptable at this time. The issues involve deviations from current good manufacturing practices. A satisfactory inspection will be required before this application may be approved.

- The product should be labeled with the epinephrine strength as it was formulated. Thus, the firm should report the epinephrine in ratios of 1.15:100,000 and 1.15:200,000 because the epinephrine amount is currently formulated with a 15% overage.

- The proprietary name that the sponsor proposed in response to the January 29, 1999, approvable letter continues to be unacceptable. The term "——" implies an original strength that was "weak". If that original strength were to be discontinued, the "——" part of the trademark could be misleading.

- The imprinting on the cartridge wears off. The Agency needs data to prove that the company is capable of manufacturing cartridges with acceptable imprinting along with samples.

Dr. D'Sa informed the sponsor of the following chemistry issue:

- The issue of overage has not been satisfactorily addressed. There is a 15% overage in the product for epinephrine. The — % loss in manufacturing has not been satisfactorily accounted for. Please provide documentation of decomposition products or other evidence of loss. Also, based on the — month stability data for three lots, the product can be granted a — month expiration date, not an — month expiration date as requested.

Dr. Blatt informed the sponsor of the following labeling issues:

- Under Pharmacodynamics section, the last two sentences should be deleted and replaced with the following sentence:

——————————————— Draft

- In the ADVERSE EVENTS SECTION, under the subheading Nervous System, insert "**facial paralysis**" between "dry mouth" and "hyperesthesia". The Agency felt it was necessary because of an adverse event that occurred in France and the sponsor did not provide detailed information.

- In the ADVERSE EVENTS SECTION, the phrase ".. ——— " was deleted. The sponsor should provide explanation.

Mr. Wayne Matelski responded that the sponsor will immediately provide data to prove that the sponsor is capable of manufacturing cartridges with appropriate imprinting and will provide samples. In future, the sponsor will provide— month stability data.

CONCLUSION:

The meeting concluded with the agreement that the sponsor will be receiving an approvable action letter on May 7, 1999, because of the above mentioned outstanding issues.

Minutes Prepared By: S. Samanta, M.D. _____

Minutes Concurred By Chair: Cynthia G. McCormick, M.D. _____

cc:
Original NDA 20-971
HFD-170/Div. Files
HFD-170/SS/C. Moody
HFD-170/ C. McCormick
HFD-170/ B.Rappaport/H.Blatt
HFD-170/A.D'Sa/P.Maturu
HFD-820/J.Gibbs/S.Koepke

Drafted by : S. Samanta 6/1/99
Revised:
Initialed:
Final:
Filed Under: NDA20971.55.MM

NDA 20-971
Minutes of Teleconference
December 18, 1998

Participants

Arent Fox Kintner Plotkin & Kahn, PLLC (Counsel to Deproco Inc., and Specialite's Septodont)
Wayne Matelski, Esq.
Brian Waldman, Esq.

Food and Drug Administration
Cynthia McCormick, M.D., Division Director
Eric Sheinin, Ph.D., Office of New Drug Chemistry Director
Steven Koepke, Ph.D., Deputy Division Director
Albinus D'Sa, Ph.D., Chemistry Team Leader
Ken Nolan, Project Manager

Objective: The Agency stated the purpose of the teleconference was to discuss its concerns noted during the review of NDA 20-971 regarding epinephrine overage specifications.

Summary of Discussion

- Pre-Approval Inspection Concerns

  The Agency requested a status update regarding the inspection date for DMF . ——— Articaine. The applicant indicated that they are unsure if —— could be ready for inspection by January 30, 1999. Reportedly, —— will be ready by either late January 1999 or early February 1999 time frame. The Agency requested an early notification of the inspection date.

- Epinephrine Tartrate Overage Concerns

  The applicant was referenced to the submission dated September 10, 1998, page 2, question 5, regarding the applicant's response to the Agency's concern on overage of epinephrine tartrate. The Agency stated the response provided in the submission was unacceptable due to the following concerns:

  - That the target formulation and the label claims should be identical. CDER's policy is to allow overages when reproducible manufacturing losses can be demonstrated but not for losses due to degradation on storage. Manufacturing losses would have to be sufficiently justified with data. The —% loss in manufacturing would need to be documented, with data on degradants of epinephrine in the drug product. The Agency explained that if this loss was due to degradation, and the specification for degradation is —%, then this does not provide any allowance for additional degradation during the shelf-life of the product.

- The applicant was informed that the specifications for epinephrine should be 90-115% of the formulation target. It was suggested that the product should be labeled to reflect the actual formulation. For example, currently the drug is formulated at 19.55μg in 1.7mL cartridges (11.5μg/mL). The specification would allow for assay to vary from 90-115% of this value. [Currently the applicant labels the product as —μg/mL or ~ μg in 1.7mL cartridges with a 15% overage. If the claimed — % manufacturing loss is, in fact, reproducible, the product can be formulated with a — % overage.]

- The impact of not formulating with an overage is that the product would probably have a shorter expiration date if it does not meet the (90-115%) specification. If the manufacturing loss is accepted by the agency, then the label claim would be revised to reflect the batch formulation assay ——— Thus, the Agency advised the applicant to formulate at label claim and not at 15% above. The Agency advised that the formulation target used in the clinical trials should be the label claim.

- An alternative approach would be for the applicant to find a way to stabilize the epinephrine to reduce degradation.

- The Agency intends to communicate with U.S.P. on the (90-115%) specification for epinephrine tartrate.

- Status of Reviews

The applicant requested that the Agency provide a status of reviews. The Agency responded:
- the reviews were progressing and that the secondary reviews were pending, and
- if problems arose during the review process we would notify the applicant in a timely manner.

- Closing Remarks

The applicant expressed its gratitude regarding the Agency's cooperation and continued assistance during the review process.

Minutes Prepared by: [signature] Chair's Concurrence: [signature] 1/15/99

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NDA 20-971
Minutes of Teleconference
December 3, 1998

Participants

Arent Fox Kintner Plotkin & Kahn, PLLC (Counsel to Deproco Inc., and Specialite's Septodont)
Wayne Matelski, Esq.
Brian Waldman, Esq.

Food and Drug Administration
Cynthia McCormick, M.D., Division Director
Bob Rappaport, M.D., Deputy Division Director
Albinus D'Sa, Ph.D., Chemistry Team Leader
Pramod Maturu, Ph.D., M.B.A., Chemist, Reviewer
Ken Nolan, Project Manager

Objective: The sponsor noted that the primary purpose for the call was:

1. to share with the Agency the status of the sponsor's discussions with [redacted] (i.e., the DMF-holder for DMF [redacted] concerning [redacted] 's availability for an FDA's pre-approval inspection and;
2. to obtain the Agency's feedback on the options available to the Sponsor in resolving the matter.

Summary of Discussion

- Nomenclature Concerns

The applicant stated it had received the Agency's letter recommending that the proposed product name Septanest® [redacted] be changed because the acronym [redacted] suggests that the product is intended for spinal use. The applicant agreed to modify the drug product's name and would be submitting a letter describing the revised name within the next few days.

- Status of Reviews Concerns

The applicant requested the Agency provide a status of the Agency's review of NDA 20-971. Dr. McCormick responded by explaining that while she has not personally seen the reviews yet, she understands that the toxicology, clinical, and chemistry reviews are proceeding smoothly and that the Agency has not identified "any stumbling blocks" at this point. Dr. McCormick indicated that the application would receive the Division's full-time review in the next few weeks. Dr. McCormick further noted that, assuming no problems

arose, she expected the Agency to take action by the end of January 1999. Dr. McCormick commented that because the application covered a new molecular entity, the application would also require approval at the Office level (i.e., Office of Drug Evaluation III), which would occur after the division completed its review in early January 1999.

- Inspection Concerns

The applicant summarized the status of their discussions with — concerning — availability for an inspection.

- Reportedly, the applicant met with a — representative to determine whether — would be ready for the FDA to inspect its — facilities during the Agency's previously scheduled inspection of the entire — plant in early December.
- It was noted that although — — acilities are in full compliance with current GMPs, the company is in the process of upgrading its facilities to include — It was explained that despite the applicant's best efforts to convince — otherwise, — has decided that it will defer FDA inspection of the — facilities until it has completed the upgrades.
- The applicant noted that during the December inspection, — does, however, intend to ask the FDA inspector briefly to review the company's planned upgrades and to provide any preliminary comments.
- The applicant stated — will be tentatively ready for an inspection at the end of January or the beginning of February 1999, and that — representatives will confirm this date on or about December 14.

The applicant acknowledged its discontent with — decision, but clarified that the drug product manufacturer, Specialite's Septodont, incorporated numerous controls in the manufacturing process that would ensure product safety. The following existing procedures were noted in regards to manufacturing process controls:

- In addition to requiring a certificate of analysis from — for each batch of articaine, Specialite's Septodont conducts its own analyses on each batch to ensure that product specifications are met. All tests identified on the — certificate of analysis are also conducted by Specialite's Septodont.
- Specialite's Septodont conducts bacterial endotoxin tests as part of its finished drug product specifications
- Specialite's Septodont's manufacturing process includes —

The applicant further noted that Specialite's Septodont would be willing to conduct bioburden and endotoxin analyses on each batch of articaine received from — if requested to do so by the Agency.

- Regulatory Action Concerns

The applicant inquired whether the Agency would consider approving the NDA prior to its inspection of — in January or February given these additional safety measures followed by Specialite's Septodont.

The chemistry team leader noted:

- unfamiliarity of instances in which inspection requirements were waived by the Agency.
- during the inspection of — the Agency inspector would focus on compliance with GMP requirements.
- that certain types of contamination of the drug substance might not be picked up in drug product testing as requested in the application..

Dr. McCormick stated that approval prior to the inspection would be "unorthodox," and was unsure whether such an approval could be granted. Dr. McCormick proposed that if the Agency was permitted to inspect — by January 30, 1999, and the assumption that the inspection was successful in addition to no other problems arose during the review of the NDA, an approval action could be granted at the end of January 1999.

However, if — did not permit the inspection until February 1999, the Agency would not be able to grant approval. Dr. McCormick suggested that the Agency would be willing to issue an approvable action at the end of January 1999. The condition of an approval action by the Agency depends on a successful inspection of —

The applicant stated its understanding of the regulatory actions pending the timeliness of the inspection and the inspection findings.

The applicant agreed to contact the Agency as soon as — confirmed an inspection date for the Agency to conduct the inspection. The applicant and the Agency agreed to discuss the options when Mr. Matelski had this updated information.

- Closing Remarks

The applicant expressed its gratitude regarding the Agency's cooperation and continued assistance during the review process.

Minutes Prepared by: /S/

Chair's Concurrence: /S/

4

DOCUMENTATION OF TELEPHONE CONVERSATION

Meeting Date: November 13, 1998

Time: 4:00 p.m.

Location: 9B-45

Application: NDA 20-971 (Deproco) Septanest and DMF [redacted]

Type of Meeting: Teleconference

Meeting Chair: Cynthia G. McCormick, M.D., Division Director

Meeting Recorder: Ken Nolan, Project Manager

FDA Attendees, titles, and Office/Division:

Cynthia G. McCormick, M.D., Division Director
Bob Rappaport, M.D., Deputy Division Director
Abi D'Sa Ph.D., Team Leader, Chemistry
Ken Nolan, Project Manager

External Attendees:

Kim Jankowitz, US Agent for [redacted]
Brian Waldman, J.D., Counsel to Specialites Septodont and Deproco Inc.

Meeting Objectives:

The Agency arranged this teleconference between the US Agent for [redacted] (DMF [redacted]), the US Agent for Deproco (NDA 20-971), and the Agency to discuss pre-approval inspection concerns. DMF [redacted] referenced in NDA 20-971.

Background: On June 29, 1998 the Agency issued an information request letter to [redacted] regarding deficiencies in DMF [redacted] including a request to respond when [redacted] would be prepared for pre-approval inspections. [redacted] responded to the Agency's letter on August 17, 1998. In a letter dated September 25, 1998 [redacted] requested a meeting to discuss pre-approval inspection issues.

Discussion Points:

- — unavailability for a preapproval inspection for NDA 20-971 prior to the regulatory goal date would prevent the Agency from taking a final approval action by January 29, 1999. It was made clear that if no other important deficiencies were identified during the final stages of review, the Agency could take an Approvable action in the absence of an inspection. The sponsor said that such an action would not be a problem.

- The sponsor attempted to make the case that an inspection may not be needed. While the sponsor was asked to submit this case for review, the Division indicated that they had no knowledge of an exception to the pre-approval inspection requirement for an NME.

- US Agent for Deproco and Septodont cited ongoing discussions between Deproco, Septodont and — regarding the inspection. The Sponsor agreed to keep the Agency informed of the earliest date on which an inspection could be scheduled.

Minutes Prepared by: /S/

Chair's Concurrence: /S/

DOCUMENTATION OF TELEPHONE CONVERSATION

Meeting Date: November 12, 1998

Time: 4:00 p.m.

Location: 9B-45

Application: NDA 20-971 (Deproco) Septanest and DMF [redacted]

Type of Meeting: Teleconference

Meeting Chair: Cynthia G. McCormick, M.D., Division Director

Meeting Recorder: Ken Nolan, Project Manager

FDA Attendees, titles, and Office/Division:

Cynthia G. McCormick, M.D., Division Director
Ken Nolan, Project Manager

External Attendees:

Kim Jankowitz, US Agent for [redacted]

Meeting Objectives:

The Agency contacted the applicant to clarify the September 25, 1998 meeting request regarding DMF [redacted] referenced in NDA 20-971 ([redacted] and to propose a teleconference between the US Agents for Deproco, the US Agent for [redacted] and the Agency.

Background: On June 29, 1998 the Agency issued an information request letter to [redacted] regarding deficiencies in DMF [redacted] including a request to respond when [redacted] would be prepared for pre-approval inspections. [redacted] responded to the Agency's letter on August 17, 1998. In a letter dated September 25, 1998 [redacted] requested a meeting to discuss pre-approval inspection issues.

Discussion Points:

- The Agency stated that [redacted] unavailability for pre-approval inspections would effect the action taken on NDA 20-971. The Agency proposed that the US Agent for Deproco, the US Agent for [redacted], and the Agency hold a teleconference on November 13, 1998 to make certain that each stakeholder was aware of what effect a delayed pre-approval inspection may have on NDA 20-971. The Agency proposed to coordinate the teleconference.

- The US Agent for [redacted] agreed to participate in the proposed teleconference.

- The US Agent for [redacted] conveyed that meetings between [redacted] non-USA representatives and Deproco's, non-USA representatives will take place next week to discuss pre-approval inspection concerns. The US Agent for [redacted] stated the Agency would be kept informed of the outcome of the meetings.

Minutes Prepared by: [redacted] /S/

Chair's Concurrence: [redacted] /S/

MEMORANDUM OF TELECONFERENCE MINUTES

Meeting Date: October 15, 1998

Time: 11:00 a.m.

Application: DMF —— , referenced in NDA 20-971 (Deproco Inc.,) Septanest

Type of Meeting: Teleconference/Information Request

FDA Attendee: Ken Nolan, Project Manager

External Attendee: Kim Jankowitz, US Agent for ——

Meeting Objectives: The Agency requested this teleconference to obtain clarification from the US Agent regarding the September 25, 1998 —— meeting request letter submitted by the European —— representatives.

Background: In response to the September 25, 1998 meeting request from the European —— representatives for DMF —— referenced in NDA 20-971 (Deproco Inc.,) Septanest, the Agency attempted to contact the US Agent for —— on October 8 and 13, 1998. Ms. Jankowitz was out of the office on both dates and voice mail messages were left with her office. On October 15, 1998, the US Agent for —— returned the Agency's telephone calls regarding the September 25, 1998 —— meeting request letter.

The following is a summarization of the October 15, 1998 teleconference between the Agency and the US Agent for ——

Initially, the US Agent for —— was unable to recollect the letter being sent by the European —— representatives for DMF —— . However, upon the Agency reciting excerpts from the September 25, 1998 letter, the US Agent for —— was able to recollect receiving a copy of the letter from the European ——representative.

The Agency requested clarification of the meeting request as to whether the DMF holder requested to discuss the preapproval inspections regarding NDA 20-971 not taken place until mid-1999 and/or to discuss facilities upgrades regarding DMF —— to comply with future GMP requirements set out in the new API-Guidance document). The US Agent for —— was unsure of the intent of the meeting request, but would contact the European —— representatives to discuss the matter.

The Agency inquired whether the US Agent for the NDA 20-971 was aware that —— facilities would not be ready for preapproval inspections. The US Agent for ——was uncertain whether the US Agent for NDA 20-971 was aware of —— unreadiness for preapproval inspections.

The Agency explained that the preapproval inspections are mandatory prior to the Agency taking an action on NDA 20-971. Additionally, the US Agent for [redacted] was informed that a mid-1999 inspection would take after the January division goal date and the March 30, 1999 PDUFA thereby impacting a possible approval action. The Agency strongly recommended that the NDA holder be informed that preapproval inspection for the [redacted] European Articaine Program will not be available for inspection until mid-1999.

The US Agent for [redacted] informed the Agency she would not return to the office on Monday, October 19, 1998 and would address these concerns with the Europe [redacted] representatives and US Agent for NDA 20-971.

The Agency reiterated that the NDA holder is made aware of the [redacted] facilities not being ready for inspection until mid-1999 as-soon-as-possible.

The attendees expressed gratitude for the teleconference.

cc: DMF — Archives
NDA 20-971 Archives
HFD-170\McCormick\Rappaport\Blatt\Moody
HFD-170\D'Sa\Maturu
HFD-170\Jean\Goheer
HFD-170\Uppoor
HFD-170\Permutt
HFD-700\Hu
HFD-170\Klein
HFD-40\Askine

Rev.November 11, 1998\McCormickc\Moody-ken

Electronic Mail Message

Date: 4/2/00 9:00:49 PM
From: Jerry Phillips (PHILLIPSJ)
To: Cynthia McCormick (MCCORMICKC)
Cc: Laura Governale (GOVERNALEL)
Cc: Lauren Lee (LEEL)
Subject: Re: Septocaine

Cynthia:

No problem with the spelling of Septocaine (was reviewed as [redacted] on the outcome. I've attached Lauren Lee's review that she completed on Friday. I concur with her conclusion that Septocaine is acceptable from OPDRA's perspective. Thanks!

Jerry

Electronic Mail Message

Date: 3/2/00 4:39:58 PM
From: Jerry Phillips (PHILLIPSJ)
Subject: OPDRA Consult #00-0058; Septanest

Laura:

In an effort to respond to your recent (2/23/00) OPDRA consult request for a tradename review for Septanest (NDA 20-971) before March 8th, i am going to respond by E-mail. You should be aware that the Office was unable to respond to this consult with it's normal review of conducting verbal and written studies because of inadequate time. Here's our opinion:

OPDRA does not recommend the approval of the proprietary name SEPTANEST. An expert panel discussion today came to the conclusion that Septanest is too phoentically similar to Citanest. Both of these products are dental products and will be prescribed/used in the same environment (dental offices). We believe that this is an unacceptable level of risk. Confusion could occur if a dentist asks for a cartridge of Septanest and is given Citanest (or vice versa) instead. We believe that there is no reason to assume this risk and ask that the firm be so ɔtified and asked to resubmit a new name. We understand that the goal ate for approval is April 3rd and OPDRA will do everything possible to meet that deadline if the firm submits a new name ASAP.

Thanks. I can be reached at 827-3246 if you want to discuss.

Jerry Phillips

Electronic Mail Message

Date: 3/3/00 2:49:28 PM
From: Harold Blatt (BLATTH)
To: Laura Governale (GOVERNALEL)
Cc: Cynthia McCormick (MCCORMICKC)
Cc: Bob Rappaport (RAPPAPORTB)
Subject: NDA 20-971 Septanest

Laura,

Regarding the concerns expressed by OPDRA about possible confusion of the names Septanest and Citanest, I believe it is unlikely that the two products will be confused. Septanest carpules have a gray stopper and gray printing whereas Citanest Plain 4%(w/o vasoconstrictor) has a black stopper and black printing and Citanest Forte 4% 1:200,000 Epinephrine has a yellow stopper and yellow printing.

Hal

Printed by Cynthia McCormick

Electronic Mail Message

.sitivity: COMPANY CONFIDENTIAL

Date: 05-May-1999 01:38pm
From: Dan Boring
BORINGD
Dept: HFD-530 CRP2 S447
Tel No: 301-827-2396 FAX 301-827-2510

: Bob Rappaport (RAPPAPORTB)
: Cynthia McCormick (MCCORMICKC)

bject: [redacted] in Trademark

nthia,

The LNC recommends against the use of [redacted] as a proprietary me term for two reasons. By using a term like "double-strength" or [redacted] you are tying yourself to some original strength that was eak". If that original strength is discontinued, the [redacted] part of e trademark continues and subsequently becomes misleading.

Additionally, we've had numerous reports over the years of [redacted] being confused with the number "forty". The result is that appropriate numbers of doses or inappropriate doses of medication have en administered.

Overall, the LNC would find the term [redacted] unacceptable for e a proprietary name designation.

thanx,
dan

E L E C T R O N I C M A I L M E S S A G E

nsitivity: COMPANY CONFIDENTIAL

Date: 20-Jan-1999 02:29pm EST
From: Dan Boring
BORINGD
Dept: HFD-530 CRP2 S447
Tel No: 301-827-2396 FAX 301-827-2510

: Kenneth Nolan (NOLANK)

bject: Re: NDA 20-971 (Deproco) Septanest

n,

It is the opinion of the Committee that the —— and '—— rve no real purpose and is misleading by not revealing both gredients contained. Simply having the product brand name followed by e strength for both ingredients is our recommendation.

dan

E L E C T R O N I C M A I L M E S S A G E

Date: 10-Sep-1998 12:42pm EDT
From: Kenneth Nolan
NOLANK
Dept: HFD-170 PKLN 9B45
Tel No: 301-443-3741 FAX 301-443-7068

TO: See Below

Subject: NDA 20-971 (Deproco) Labeling and Nomenclature Comm. Response

I have forwarded to you a copy of the Labeling and Nomenclature Committee's concerns regarding NDA 20-971 (Deproco) Septanest.

If you should have any questions regarding this matter please let me know.

Ken

Distribution:

TO:	Cynthia McCormick	(MCCORMICKC)
TO:	Bob Rappaport	(RAPPAPORTB)
TO:	Harold Blatt	(BLATTH)
TO:	Corinne Moody	(MOODY)
TO:	Albinus D'Sa	(DSAA)
TO:	Pramoda Maturu	(MATURU)
TO:	Dou Jean	(JEAN)
TO:	Anwar Goheer	(GOHEER)
TO:	Venkata Ramana Uppoor	(UPPOORR)
TO:	Chuanpu Hu	(HUC)
TO:	Thomas Permutt	(PERMUTTT)
TO:	Michael Klein	(KLEINM)
TO:	Mark Askine	(ASKINEM)
TO:	Thomas Abrams	(ABRAMST)
TO:	Mathew Thomas	(THOMASM)
TO:	Charles Snipes	(SNIPESC)
TO:	Brenda Uratani	(URATANIB)

E L E C T R O N I C M A I L M E S S A G E

Date: 19-Jan-1999 02:54pm EST
From: Pramoda Maturu
MATURU
Dept: HFD-170 PKLN 9B32
Tel No: 301-443-4250 FAX 301-443-4935

O: Michael Theodorakis (THEODORAKIS)

C: Albinus D'Sa (DSAA)
C: John Gibbs (GIBBS)
C: Cynthia McCormick (MCCORMICKC)

ubject: Addendum to che rev #2 dated 12.8.98 for NDA 20971, Articaine

s agreed in todays meeting, the addendum responds to the comments of Abi D'Sa ated 12.26.98 to chem review #2 dated 12.8.98 for NDA 20971 Articaine by making eference to EES, e-mail messages on epinephrine overage, and telecon between ne applicant and review division.

is acceptable for 2 Mfg. sites (Specialites Septodont and [redacted] and ing for one Mfg. site (

xpiry date for Articaine drug product is [redacted] months, as per telcons between the pplicant and review division. Expiry date was based on the time estimate for [redacted]% of the input for epinephrine, and request for [redacted]% overage for epinephrine to over manufacturing loss was not granted for lack of evidence as to where the [redacted]% ent, as per Dr. Eric Sheinin.

APPEARS THIS WAY
ON ORIGINAL

E L E C T R O N I C M A I L M E S S A G E

Sensitivity: COMPANY CONFIDENTIAL

Date: 16-Dec-1998 10:24am EST
From: Albinus D'Sa
DSAA
Dept: HFD-170 PKLN 9B45
Tel No: 301-443-3741 FAX 301-443-7068

TO: Pramoda Maturu (MATURU)

Subject: FWD: Epinephrine HCl

E L E C T R O N I C M A I L M E S S A G E

Sensitivity: COMPANY CONFIDENTIAL

Date: 14-Dec-1998 06:07pm EST
From: Albinus D'Sa
DSAA
Dept: HFD-170 PKLN 9B45
Tel No: 301-443-3741 FAX 301-443-7068

TO: Frank Holcombe (HOLCOMBE)

Subject: Epinephrine HCl

Frank:

Could you please help me with a question pertaining to overage. What overage is permitted in OGD for anesthetic products that contain epinephrine HCl or bitartarate salt?

USP has a 90-115% specification limit for ephineprine dental anesthetic products, do you know why the specs were expanded from the 90-110%?

We have a product that is a new anesthetic (articaine HCl and epinephrine bitartarate) that has an overage of 15% for epinephrine, approximately —% of which is lost in manufacturing, that leaves a— % overage to extend the expiration dating of the product. Do you have any similar experience in OGD?

Hope you can provide some feedback.

Abi

E L E C T R O N I C M A I L M E S S A G E

Sensitivity: COMPANY CONFIDENTIAL

Date: 16-Dec-1998 10:22am EST
From: Albinus D'Sa
DSAA
Dept: HFD-170 PKLN 9B45
Tel No: 301-443-3741 FAX 301-443-7068

TO: Pramoda Maturu (MATURU)

Subject: FWD: RE: Epinephrine HCl

APPEARS THIS WAY
ON ORIGINAL

E L E C T R O N I C M A I L M E S S A G E

Sensitivity: COMPANY CONFIDENTIAL

Date: 15-Dec-1998 08:54am EST
From: Frank Holcombe
HOLCOMBE
Dept: HFD-640 MPN2 E278
Tel No: 301-827-5849 FAX 301-443-3839

TO: Albinus D'Sa (DSAA)

Subject: RE: Epinephrine HCl

Abi,

I don't know the history of the 115% upper limit for epinephrine solutions, but that limit goes back at least to 1985. My guess is that USP set it that high in recognition of the instability of epinephrine solutions that weren't borates.

So far as an overage, we generally would not accept the 15% you mentioned, unless the generic could demonstrate to us through comparative testing that the reference listed drug also contained that overage. The —% manufacturing loss might be accepted but not as a manufacturing loss unless there was some demonstration that it was in fact a loss, and not just degradation during production.

We generally don't allow overages if they are "corrections" to adjust for stability problems. We would expect formulation to the label quantity, but might accept a overage of a few percent if the manufacturing results are low. But as described below, there are exceptions.

My guess is that for an ANDA, if the applicant proposed the —% (stability) plus —% (manufacturing loss) overage, we would ask where the —% went, and to see reference listed drug testing to justify the other —%. We would then use the testing results to set the allowable upper limit.

Frank

Electronic Mail Message

Date: 3/14/00 5:48:33 PM
From: Carol Pamer (PAMERC)
To: See Below
Subject: Additional comments: OPDRA Consult #00-0058; Septanest

In follow-up to today's meeting regarding Septanest, these are the additional safety concerns I made during the meeting, particularly concerning the proposed proprietary name. A full review and formal consult was not completed previously, due to time constraints. However, our email reply is attached which noted our concerns with the initial consideration of the trade name.

1. The availability of a Citanest Plain (e.g. No epinephrine) and the fact that both Septanest products contain epi could be the cause of a serious adverse event. Since a patient on an MAOI or MAOI-like drug could be inadvertantly administered Septanest containing epi. Note in product labeling for Nardil that local anesthetics with vasoconstrictors are contraindicated in patients on Nardil, for example.

2. Patient allergy to the active or inactive ingredients in either 'uct could be a concern, if a patient receives the wrong product.

3. Since this is a professional product approved for use in dentistry, there will be some control over its distribution. However, both Citanest and Septanest will likely be stored in the same location. Although we have not had the opportunity to review the packaging configuration for Citanest, if the cartridges appear similar and can be loaded into the same injector, errors could still occur.

4. Postmarketing spontaneous reporting of adverse events is generally lower in Canada versus the U.S. The data the sponsor is planning to provide on potential errors in Canada where both Citanest and Septanest are available may not pick up that signal.

In the case of other products, we have made suggestions for Phase IV commitments from sponsors regarding names; we could discuss those further, perhaps after the the sponsor responds. But as in our original response, we object to the use of the name Septanest.

We thank you for the opportunity to participate in the meeting and offer input regarding these concerns.

Sincerely,

Carol Pamer, R.Ph.
Safety Evaluator, Med Errors Staff