CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
20-971

Chemistry Review(s)

DIV. OF ANESTHETIC CRITICAL CARE & ADDICTION DRUG PRODUCTS
(HFD-170)

DATA SUMMARY SHEET

NDA# 20-971 REVIEW # 6 REVIEW DATE: 3.29.2000
Primary and secondary user fee goal dates are 3rd April 2000, and 3rd June 2000.

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE
Amendment	3.22 2000	
Amendment	3.16.2000	

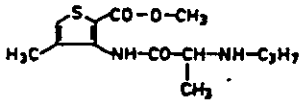
APPLICANT & ADDRESS OF APPLICANT:
Deproco Inc, c/o Arent Fox Kinter Plotkin & Kahn, 1050 Connecticut Ave, Washington, DC 20036-5339.

DRUG PRODUCT NAME(S):
Proprietary: Septanest
Nonproprietary/USAN: Articaine HCl 4% with Epinephrine 1:100,000 and 1:200,000. Solution for injection
Code Name/#:
Chem Type/Ther.Class: 1 S (filed as 500(b)(2)

PHARMACOL CATEGORY/INDICATION: for use in dental anesthesia
DOSAGE FORM(S): 1.7 ml glass cartridges with — closures.

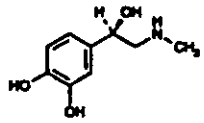
ROUTE/ADMIN: Parental
DISPENSED: X Rx __ OTC
CHEMICAL NAME/STRUCTURAL FORMULA

Articaine. $C_{13}H_{20}N_2O_3S$. 284.38. [Carticaine is BAN.] 4-Methyl-3-[2-(propylamino)propionamido]-2-thiophenecarboxylic acid, methyl ester. *CAS-23964-58-1*. INN. *Hoe 045*



Articaine HCl is a racemic mixture of two enatiomers due to a center of asymmetry. Its, pKa is 7.9, and it exists in solid sate in 2 polymorphic forms with melting points 170 C and 105 C. It is hydrolyzed by serum esterase.

Epinephrine (ep i nef' rin). USP. $C_9H_{13}NO_3$. 183.21. [Adrenaline is BAN; Epinephrine Hydrochloride is JAN.] (1) 1,2-Benzenediol, 4-[1-hydroxy-2-(methylamino)ethyl]-, (*R*)-; (2) (−)-3,4-Dihydroxy-α-[(methylamino)methyl]benzyl alcohol. *CAS-51-43-4*. INN; JAN. *Adrenergic* (*vasoconstrictor*). Adrenalin (Parke-Davis); Adrenalin in Oil (Parke-Davis†); (Astra); (Bristol-Myers Squibb†); Bronkaid Mist (Sterling Health U.S.A.); (Ciba Vision Ophthalmics); (Elkins-Sinn); Epifrin (Allergan); Glaucon (Alcon); Primatene Mist (Whitehall-Robins); Sus-Phrine (Forest); (Wyeth-Ayerst); component of Citanest Forte (Astra)



Epinephrine Bitartrate. USP. $C_9H_{13}NO_3.C_4H_6O_6$. 333.30. (1) 1,2-Benzenediol, 4-[1-hydroxy-2-(methylamino)ethyl]-, (*R*)-, [*R*-(*R**,*R**)]-2,3-dihydroxybutanedioate (1:1) (salt); (2) (−)-3,4-Dihydroxy-α-[(methylamino)methyl]benzyl alcohol (+)-tartrate (1:1) salt. *CAS-51-42-3; CAS-51-43-4* [epinephrine]. JAN. *Adrenergic* (*ophthalmic*). Asmatane Mist (3M Pharmaceuticals†); Bronitin Mist (Whitehall-Robins†); Bronkaid Mist Suspension (Sterling Health U.S.A.); Epitrate (Wyeth-Ayerst); Medihaler-Epi (3M Pharmaceuticals); Primatene Mist Suspension (Whitehall-Robins); Suprarenin (Sterling Winthrop†); component of Asthmahaler (Menley & James); component of E-Pilo (Ciba Vision Ophthalmics)

RELATED DOCUMENTS:

1) DMF —
2) DMF — y
3) DMF — for supplied by
4) DMF — for supplied by —
5) DMF —
6) IND — a predecessor for this NDA.

CONSULTS:

1. Mfg. sites are acceptable to compliance, as per EES dated 22 February 2000. The drug product is manufactured by Specialites Septodont, Paris, France (CFN# 9610964).
2. — sterilization process was acceptable to microbiologist, Dr. Brenda Utrani, as per micro consult dated 10.28.98.
3. Trade name Septanest is acceptable to CMC discipline, labeling and nomenclature committee and unacceptable to OPDRA, as per response dated 2 March 2000 for the consult#00-0058.
4. — has completed MV work on 10.24,98 with no major problems except for the following 4 comments: (i) the need for a separate resolution solution with a process impurity while performing assay, (ii) the need to include peaks areas due to mobile phase for % impurity determination. (iii) the need for recording the IR spectrums for Articaine base as reference spectrum, and (iv) the need for the inclusion of drying time in LOD test. MV work is in progress at —

REMARKS/COMMENTS:

This review addresses sponsors response to labeling issues raised by the agency during several recent teleconferences, such as, (1) sample cartridges of the Septanest injections, (2) test methods to assure that printing of cartridges can not be rubbed off, (3) copies of can label, box label, (4) appropriate warning statement for sulfites in injections on the label.

Q. (1) Sample cartridges of the Septanest injections.

R (1): Sample glass cartridges in blue and colors were submitted. Blue imprint color is for Septanest 1:100,000 .

Comment: Need "Injection" after Articaine with Epinephrine on glass cartridges.

Q. (3) Copies of can label, box label,
Q. (4) Appropriate warning statement for sulfites in injections on the label.

R. (3) and (4) Color copies of can labels, box labels were submitted for Septanest 1:100,000 .

1 pages redacted from this section of the approval package consisted of draft labeling

Comment: Prominence of Articaine is not adequate. Prominence of Articaine and white space between Septanest and Articaine needs to be changed. Warning for sulfite needs to be more prominent. 21 CFR 201.22 labeling requirement is for prescription drugs containing sulfites.

Q. (2) Test methods to assure that printing of cartridges can not be rubbed off,

R. (2): Sponsor has contacted the cartridge manufacturer, [redacted] and provided [redacted] response. [redacted] states that [redacted] the glass and these inks will not be rubbed off.

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ON ORIGINAL

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Conclusions and recommendations: Articaine HCl 40mg/ml with 15% overage for epinephrine with label stating 1:100,000 and 1:200:000, is formulated in isotonic sterile aqueous solution for local anesthesia in dentistry. Epinephrine being oxygen sensitive its stability is improved by the addition of sodium metabisulfite antioxidant at 0.5mg/ml. There are about 30 injection drug products that contain sulfites, as per PDR search. Isotonicity was adjusted with sodium chloride at 1.6mg/ml. The cartridge intended for US marketing has 1.7ml fill volume and [redacted] seals. Septanest products sold in UK have a different fill volume, 2.2 ml, as per exhibit sample supplied on 16th March 2000. Blue imprint color is for Septanest 1:100,000 [redacted] The drug product is made in France by Specialites Septodont and distributed in US by Septodont Inc US. The sponsor has adequately addressed CMC deficiencies listed in second approvable letter dated 7th March 1999, and in subsequent recent teleconferences. Chemistry review#5 dated 3.8.2000 has commented on the responses to questions in second approvable letter dated 7th March 2000.

The communication to sponsor has to include the following 5 points.

(1) Prominence of Articaine is not adequate.
(2) Prominence of Articaine and white space between Septanest and Articaine needs to be changed.
(3) Warning for sulfite needs to be more prominent.
(4) Need "Injection" after Articaine with Epinephrine on glass cartridges.
(5) Explanation provided for the durability of imprinting is acceptable in lieu of ASTM method

/S/

Dr. P.Maturu, PhD, Primary review Chemist

/S/

Dr. A.D'Sa, PhD, Chemistry Team Leader

CC:
Orig. NDA 20971
HFD-170/Division File, PMaturu, ADSa, LGovernale,
HFD-820/SKoepke
File Name: c:\n20971r6.200.doc
ADEQUATE

DIV. OF ANESTHETIC CRITICAL CARE & ADDICTION DRUG PRODUCTS (HFD-170)

DATA SUMMARY SHEET

NDA# 20-971 **REVIEW # 5** **REVIEW DATE: 3.8.2000**
Primary and secondary user fee goal dates are 3rd April 2000, and 3rd June 2000.

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE
Amendment	2.28 2000	
Amendment	2.3.2000	
Briefing package	9.15.1999	

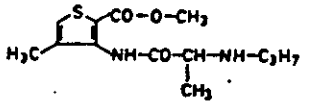
APPLICANT & ADDRESS OF APPLICANT:
Deproco Inc, c/o Arent Fox Kinter Plotkin & Kahn, 1050 Connecticut Ave, Washington, DC 20036-5339.

DRUG PRODUCT NAME(S):
Proprietary: Septanest
Nonproprietary/USAN: Articaine HCl 4% with Epinephrine 1:100,000 and 1:200,000. Solution for injection
Code Name/#:
Chem Type/Ther.Class: 1 S (filed as 500(b)(2)

PHARMACOL CATEGORY/INDICATION: for use in dental anesthesia
DOSAGE FORM(S): 1.7 ml glass cartridges with [redacted] closures.

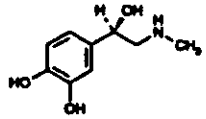
ROUTE/ADMIN: **Parental**
DISPENSED: X Rx __ OTC
CHEMICAL NAME/STRUCTURAL FORMULA

Articaine. $C_{13}H_{20}N_2O_3S$. 284.38. [Carticaine is BAN.] 4-Methyl-3-[2-(propylamino)propionamido]-2-thiophenecarboxylic acid, methyl ester. *CAS-23964-58-1*. INN. *Hoe 045*



Articaine HCl is a racemic mixture of two enatiomers due to a center of asymmetry. Its, pKa is 7.9, and it exists in solid sate in 2 polymorphic forms with melting points 170 C and 105 C. It is hydrolyzed by serum esterase.

Epinephrine (ep i nef' rin). USP. $C_9H_{13}NO_3$. 183.21. [Adrenaline is BAN; Epinephrine Hydrochloride is JAN.] (1) 1,2-Benzenediol, 4-[1-hydroxy-2-(methylamino)ethyl]-, (*R*)-; (2) (−)-3,4-Dihydroxy-α-[(methylamino)methyl]benzyl alcohol. *CAS-51-43-4*. INN; JAN. *Adrenergic (vasoconstrictor)*. Adrenalin (Parke-Davis); Adrenalin in Oil (Parke-Davis†); (Astra); (Bristol-Myers Squibb†); Bronkaid Mist (Sterling Health U.S.A.); (Ciba Vision Ophthalmics); (Elkins-Sinn); Epifrin (Allergan); Glaucon (Alcon); Primatene Mist (Whitehall-Robins); Sus-Phrine (Forest); (Wyeth-Ayerst); component of Citanest Forte (Astra)



Epinephrine Bitartrate. USP. $C_9H_{13}NO_3.C_4H_6O_6$. 333.30. (1) 1,2-Benzenediol, 4-[1-hydroxy-2-(methylamino)ethyl]-, (*R*)-, [*R*-(*R,*R**)]-2,3-dihydroxybutanedioate (1:1) (salt); (2) (−)-3,4-Dihydroxy-α-[(methylamino)methyl]benzyl alcohol (+)-tartrate (1:1) salt. *CAS-51-42-3; CAS-51-43-4* [epinephrine]. JAN. *Adrenergic (ophthalmic)*. Asmatane Mist (3M Pharmaceuticals†); Bronitin Mist (Whitehall-Robins†); Bronkaid Mist Suspension (Sterling Health U.S.A.); Epitrate (Wyeth-Ayerst); Medihaler-Epi (3M Pharmaceuticals); Primatene Mist Suspension (Whitehall-Robins); Suprarenin (Sterling Winthrop†); component of Asthmahaler (Menley & James); component of E-Pilo (Ciba Vision Ophthalmics)**

RELATED DOCUMENTS:

1) DMF [redacted]
2) DMF [redacted]
3) DMF [redacted] for [redacted] supplied by [redacted]
4) DMF [redacted] for [redacted] s supplied by [redacted] Pharma.
5) DMF [redacted]
6) IND [redacted] a predecessor for this NDA.

CONSULTS:

1. Mfg. sites are acceptable to compliance, as per EES dated 22 February 2000. The drug product is manufactured by Specialites Septodont, Paris, France (CFN# 9610964).
2. [redacted] sterilization process was acceptable to microbiologist, Dr. Brenda Utrani, as per micro consult dated 10.28.98.
3. Trade name Septanest is acceptable to CMC discipline, labeling and nomenclature committee and unacceptable to OPDRA, as per response dated 2 March 2000 for the consult#00-0058.
4. [redacted] has completed MV work on 10.24,98 with no major problems except for the following 4 comments: (i) the need for a separate resolution solution with a process impurity while performing assay, (ii) the need to include peaks areas due to mobile phase for % impurity determination. (iii) the need for recording the IR spectrums for Articaine base as reference spectrum, and (iv) the need for the inclusion of drying time in LOD test. MV work is in progress at [redacted]

REMARKS/COMMENTS:

This review addresses sponsors response to our second Approvable (AP) letter dated 7th May 1999. The sponsors responses to deficiencies 1-4 are CMC issues, deficiencies 5and 6 are clinical issues, and deficiency 7 is a DDMAC issue. CMC deficiencies relate to CGMP status of Specialites Septodont mfg site, and epinephrine overage and labeling of the overage. These CMC deficiencies, responses to CMC deficiencies and reviewer comments are compiled below to support CMC approval recommendation, except for the trade name, ——

CMC deficiency #1

1) Recently, the FDA conducted an inspection of your drug product manufacturing facility, Specialites Septodont, located at Saint Maur De Fosses, Paris, France for conformance with current good manufacturing practices (cGMP). The inspection report (5/5/1999) 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.

Applicant's response to CMC deficiency #1

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CMC deficiencies #2 and 3

2) 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 (based on a 10% overage) as you requested.

3) The product should be labeled with the epinephrine strength as it was formulated. Thus, you 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.

Applicant's response to deficiencies # 2 and 3:

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CMC deficiency #4:

4) The proprietary name that you have 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.

   Additionally, the agency has had numerous reports over the years of "—" being confused with the number "forty". Consequently, inappropriate doses or inappropriate numbers of doses of medication have been administered.

In addition, it will be necessary for you to submit revised draft labeling for the drug. The labeling should be identical in content to the enclosed labeling (text for the package insert).

Applicant's response to deficiency #4:

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ON ORIGINAL

2 pages redacted from this section of the approval package consisted of draft labeling

Reviewer's comment: To comply with CFR, revise the cartridge label with a phrase 'Contains sodium metabisulfite' To comply with USP, revise container labels storage temperature to 'store at 25C with brief excursions permitted between 15 and 30C. Brand name Septanest, requires revision to eliminate phonetic similarity with other local anesthetic products used in dentistry. Septanest trade name is acceptable to CMC discipline and labeling and nomenclature committee and unacceptable to OPADRA for phonetic similarity to Citanest. See attached response for OPADRA consult #00-0058.

Date: 02-Mar-2000 04:39pm
From: Jerry Phillips
PHILLIPSJ
Dept: HFD-400 PKLN 15B03
Tel No: 301-827-3242 FAX 301-480-8173

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 notified and asked to resubmit a new name. We understand that the goal date 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

Summary: NDA action package consists of five chemistry reviews, DMF reviews, three manufacturing sites inspection, methods validation work at two FDA labs, micro consult review, OPDRA trade name consult, and EA review. See following pages for the quantitative composition, stability test results for [redacted] years at [redacted] and [redacted] months at [redacted] and chromatograms for epinephrine at [redacted] months retest point and at release point. Methods verification was completed at one lab and still in progress at another lab. Categorical exclusion requested under 21 CFR 25.31 (b) was granted based on demand forecast of [redacted] cartridges which translates to lee than 1 ppb Articaine entry into acquatic compartment.

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Conclusions and Recommendations: Articaine HCl 40mg/ml with 15% overage for Epinephrine with label stating 1:100,000 and 1:200,000 is formulated in isotonic sterile aqueous solution for local anesthesia in dentistry. Articaine is a racemic mixture of two enantiomers. Polymorphism issue of Articaine has no impact for aqueous solution formulation. Epinephrine was added to the formulation so as to prolong the duration of Articaine's anesthesia. Epinephrine being oxygen sensitive, its stability is improved by the addition of sodium metabisulfite antioxidant at 0.5mg/ml. Isotonicty was adjusted with sodium chloride at 1.6mg/ml. The compositions intended for US marketing have no sodium edetate to eliminate paresthesia issue. The package intended for US marketing has [redacted] components to eliminate safety concerns associated with [redacted] seals. Biological and physicochemical test results were submitted for [redacted] to show compliance with USP (381) for elastomeric closures for injections. Glass cartridges were tested for compliance with EP and USP for type I glass containers. Degradation products for Articiane and Epinephrine, assay for Articaine and Epinephrine, identity for Articaine and Epinephrine, pH, mean volume and appearance test results were within specifications for [redacted] months storage at [redacted] and for [redacted] months storage at [redacted]. Same 15% epinephrine overage was used in Phase III clinical testing. Sponsor has certified for lack of patent infringement for the drug product for its intended use. Methods validation testing with lots 2G9501 and 2G9401 was completed at [redacted] but still pending at [redacted].

Sponsor has agreed for [redacted] s to prevent easy rub off of the label. Sponsor has adequately addressed the four CMC deficiencies listed in Approvable letter dated 7thMay 1999.

The action letter has to include the following information.

1) To comply with CFR, the cartridge container label requires the phrase 'Contains sodium metabisulfite'. To comply with USP, revise container labels storage temperature to 'store at 25C with brief excursions permitted between 15 and 30C. .Brand name Septanest, requires revision to eliminate phonetic similarity with other local anesthetic products used in dentistry

2) Please submit test method to assess 'rub off easiness' of the printing process for glass cartridges.

P.Maturu, PhD, Primary Review Chemist

/S/ 3/13/00

A.D'Sa, PhD, Chemistry Team Leader

cc:
Orig. NDA 20971
HFD-170/Division File, PMaturu, AD'Sa, JGIBBS
R/D Init. by
File name: c:\n20971r5.200.doc

DIV. OF ANESTHETIC CRITICAL CARE & ADDICTION DRUG PRODUCTS
(HFD-170)

DATA SUMMARY SHEET

NDA#: 20-971 REVIEW # 4 REVIEW COMPLETION DATE: Rev 5.6.99

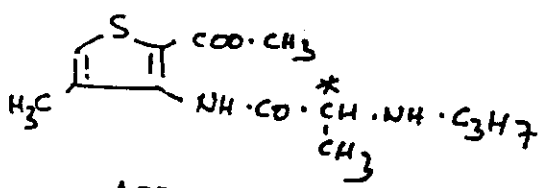
SUBMISSION TYPE	DOCUMENT DATE	CDER DATE
Correspondence (C	3.9.99	
Correspondence (C	5.4.99	
Telecon	5.6.99	

APPLICANT & ADDRESS OF APPLICANT:
Specilaities Septodont, 58 Rue Du Pont de Creteil, 94107 Saint-Mauer-des-Fosses, Paris, France 94100. US Agent for counsel, Wayne H. Matleski, Esq., of law firm Arent Fox Kinter Plotkin & Kahn, 1050 Connecticut Ave, Washington, DC 20036-5339, tel 202-857-6340. .

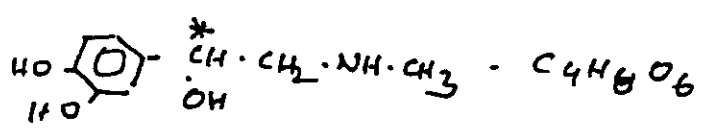
DRUG PRODUCT NAME(S):
Proprietary: Septanest [redacted] and Septanest [redacted]
Nonproprietary/USAN: Articaine HCl (40mg/ml) with Epinephrine bitartrate ([redacted] Based on 15% overage for epinephrine, the inputs are equivalent to 5.75 and 11.5ug/ml epinephrine free base. Proposed limits
Code Name/#: CAS# 23964-57-0
Chem Type/Ther.Class: 1 S

PHARMACOL CATEGORY/INDICATION:Infiltration anesthesia and nerve block anesthesia in clinical dentistry
DOSAGE FORM(S): Carpule; glass, [redacted] cartridge containing local anesthetic solution; cartridge is designed to fit in a special syringe for hypodermic injection; SVT; 1.7 ml fill; [redacted]

ROUTE/ADMIN: Parental
DISPENSED: X Rx __ OTC
CHEMICAL NAME/STRUCTURAL FORMULA/EMPIRICAL FORMULA/MOLECULAR WEIGHT:
Articaine is 4-methyl-3-(2-(propylamino)-propionamido)-2-thiophene carboxylic acid, methyl ester hydrochloride. Articaine has a center of asymmetry, pKa of 7.9, and it exists in solid sate in 2 polymorphic forms with melting points 170 C and 105 C.
See USP 23 page 595 for Epinephrine bitartrate.



ARTICAINE
* CENTER OF ASYMMETRY



EPINEPHRINE BITARTRATE
MW = 333.3

RELATED DOCUMENTS:

DMF [redacted] DMF [redacted] is now adequate, as per review dated 4 Dec 98.

DMF [redacted] DMF [redacted] was found to be adequate (OGD/HFD-630/Karen Bernard's review dated 2.25.1993).

CONSULTS:

1. Except for Specilites Septodont mfg. site, CFN#9610964, other mfg sites are acceptable to compliance. Unacceptability of Septodont site was communicated in a fax dated 5.4.99 based on inspections dated 4.30.99 by Richard Friedman and Raymond Oji. Withhold approval recommendation was based on [redacted] contamination problems, failure to [redacted] for Septanest lot RDV/3B was [redacted] failure to validate the integrity of [redacted] validation was performed at [redacted] than actual commercial batches, failure to forward some ADR complaints, etc.
2. The [redacted] sterilization process was acceptable to microbiologist, Dr. Brenda Utrani, as per micro consult dated 10.28.98.
3. MV work is in progress at [redacted] However, [redacted] has completed MV work on 10.24,98 with no major problems except for the following 4 comments: (i) the need for a separate resolution solution with a process impurity while performing assay, (ii) the need to include peaks areas due to mobile phase for % impurity determination. (iii) the need for recording the IR spectrums for Articaine base as reference spectrum, and (iv) the need for the inclusion of drying time in LOD test.

REMARKS/COMMENTS:

Correspondence dated 5.4.99 are in response to agency's concern the cartridge label rubs off during normal use. The response consisted of 3 inputs: samples of cartridge using [redacted], a certification from Mr. Jacques Barriere that cartridges for the US market will be by [redacted] and a communication on [redacted] process from the glass cartridge supplier, [redacted] did not rub off and these labels are acceptable to Septanest team members, myself, Abi D'Sa and Hal Blatt.

In a telecon dated 5.6.99 initiated by FDA, Mr. Jacques Barriere, Industrial Manager, has verbally assured that Septanest samples for the US market will look like [redacted] samples. Tel no. 01-49-76-70 00.

Correspondences dated 3.9.99, is incorrectly listed without IC code for chemistry review. 3.9.99 response has several attachments.

Attachment A: In response to FDA issue no 1, a communication dated 2.10.99 from OC, Richard Friedman, OC, to [redacted] stating that [redacted], is acceptable as [redacted] supplier.

Attachment B: In response to FDA issue no 2, revised container labels with the inclusion of a statement ' contains sodium metabisulfite'.

In response to FDA issue no 3, a statement of an intention to revise the imprinting process for the containers. The revised imprint process, ink contains [redacted] is not okay as a phase IV commitment to several members of Septanest team, as per internal divisional meeting dated 4.27.99 and 5.5.99. The applicant has to provide exhibit samples to show printing will not rub off.

Attachment C: In response to FDA issues nos. 4 and 6, revised container labels are submitted with proposed names Septanest [redacted]

COMMENT: To reflect epinephrine input, the FPL requires a revision to 1.15: 100,000 and 1.15: 200,000, Proposed names, Septanest [redacted] are unacceptable to the team members. The Clinical Division Director conveyed this internal decision in a telecon to sponsor dated 5.5.99.

In response to FDA issue no 5, revised acceptance limits for the drug product with the inclusion of NMT [redacted]% limit for articainic acid, NMT [redacted] for adrenochrome, and NMT [redacted] % total epinephrine decomposition products. However, these decomposition products were not monitored during stability study of the drug product packaged with [redacted] (12.1.98, amendment).

Attachment: In response to FDA issue no 7 on overage for epinephrine, a copy of USP23 monograph for Lidocaine with Epinephrine Injection with acceptance limits 90-115% for Epinephrine. Resubmitted a table with epinephrine concentration before [redacted] after [redacted] for 10 batches of each potency of the drug product to show about [redacted] loss in manufacturing. Resubmitted competitor product analysis to show overages for epinephrine, 10% epinephrine overage in Septodont Lignospan Standatrd and Lignospan Forte, and 13% epinephrine overage in Novocol Lidocaine with Epinephrine.

In the context of overages for epinephrine, the applicant has submitted 1953 correspondence between USP and Parke Davis, comparing calorimetric assay of epinephrine with bioassay. And a proposal to study published paper chromatography method for epinephrine

Attachment G: In response to FDA issue no 8, FPL for the drug products are submitted with Septanest [redacted] names. Made in France by Specialites Septodont, Distributed by Septodont Inc, New Castle, Delaware, USA. (see TL. memo)

Attachment H: In response to FDA issue no 9, updated marketing history with sales of about [redacted] cartridges, and only 39 patients with ADRs, for the time period 1989-1998.

Epinephrine loss in solution is complex and initial rate of epinephrine loss is a function of dissolved oxygen and epinephrine concentration. For these reasons, it is difficult to extrapolate epinephrine values from [redacted] months to [redacted] months. [redacted] months stability update is scheduled for 4.27.99 for 3 lots of each potency packaged with [redacted] Mean epinephrine data for 6 lots submitted in Dec 98 has shown 0.5% epinephrine loss during the first [redacted] months, 1.2% epinephrine loss during the subsequent [redacted] months, and 2.6% epinephrine loss during the subsequent [redacted] months. 115% epinephrine input has shown at 110% epinephrine at release and only 103% epinephrine at [redacted] months, that is, 10% epinephrine loss in [redacted] months storage.

CONCLUSIONS/RECOMMENDATIONS:

Recommendation is to withhold approval of CMC section based on the following inputs:

(i) The unacceptability of mfg. site. for Septanest to OC,

(ii) The unacceptability of proposed labeling of the epinephrine inputs, 1:100,000 and [redacted] and unacceptability of trade names, Septanest and [redacted] because with the same articaine levels it is misleading to claim one as [redacted]

(iii) The unacceptability of 5% epinephrine mfg. loss documentation,

(iv) Only [redacted] months stability at [redacted] for Septanest packaged with [redacted] s from [redacted] (12.1.98 amendment) without the decomposition products to support [redacted] months expiry date request.

[redacted] months stability update will be about 4.27.99, and without seeing the [redacted] months data for epinephrine degradation, my recommendation is to defer further discussions.

CMC section will be considered adequate with OC recommendation for approval for Septanest mfg. site, the applicant revises container labels to reflect actual epinephrine inputs, 1.15: 100,000 and 1.15: 200,000, and revises trade names to something acceptable to Septanest team members, and provides a clarification that the [redacted] glass [redacted] process is for empty glass containers prior to bulk liquid filling.

A note to CSO: A standard Methods Validation paragraph has to be included in the letter to the firm. (3).

/S/ 5.6.99
P.Maturu, PhD, Primary Review Chemist

/S/ 5/6/99
A.D'Sa, PhD, Chemistry Team Leader

cc:
Orig. NDA 20971
HFD-170/Division File
HFD-170/PMaturu, AD'Sa, JGIBBS
R/D Init. by
File name: c:\n20971r4.99
INADEQUATE

4

Memo to the file: NDA 20-971 (attached to review #3)
From : Albinus D'Sa, Ph.D. 5/4/99

The NDA has the following issues pending:

1) Inspections: Even though the Establishment Evaluation System (EES) displays an acceptable evaluation from the office of compliance, the drug product manufacturing facility, Specialities Septodont, located at Saint Maur des Fosses, Paris, France was reported to be unacceptable at this time (5/5/1999). The issues involve lack of monitoring of endotoxin. Office of compliance has recommended a withold approval recommendation. Chemistry review division concurs with this recommendation.

2) Overage: An internal ONDC meeting was held to address the issue of overage on 5/26/99, followed by a clinical division meeting dated 5/27/99. In both of these meetings, the applicants proposals were discussed. And in compliance with ONDC policy on overage, the following was noted: The applicant has not satisfactorily addressed the issue of overage. The applicant has a 15% overage in the product for epinephrine. The applicant has not satisfactorily accounted for the— % loss in manufacturing. The applicant needs to provide evidence for the loss in terms of decomposition products or other evidence of loss. The applicant's request for allowance of a —% overage with an —-month expiration dating period for the drug product is also denied. Based on the — -month stability data for 3 lots, provided by the applicant, the product can be granted a —-month expiration date.

3) Product Container Label and package insert: The name and the container label are unacceptable. The name —— is misleading at best. Also the applicant 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 which should be the labeled amount.

The applicant has satisfactorily addressed the imprint isssue. However, an advice letter should be sent separately to the applicant conveying the methods validation issues.

I concur.

/S/ 5/7/99

DIV. OF ANESTHETIC CRITICAL CARE & ADDICTION DRUG PRODUCTS (HFD-170)

DATA SUMMARY SHEET

NDA#: 20-971 **REVIEW # 3** **REVIEW COMPLETION DATE:** 4.19.99

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE
Correspondence (C	2.8.99	2.8.99, a reiteration of issues relating to overage for epinephrine, and no new CMC information to review.
Correspondence (C	2.5.99	2.5.99, notification of intent to file an amendment with a partial response addressing issues relating to overage for epinephrine.
Correspondence (C	1.7.99	1.7.99, a copy of letter from USAN dated 30th Sept 98, to inform US adopted name as Articaine hydrochloride and code designation HOE 045.
Correspondence (C	12.8.98	12.8.98, proposed new proprietary names, Septanest —

APPLICANT & ADDRESS OF APPLICANT:
Specilaities Septodont, 58 Rue Du Pont de Creteil, 94107 Saint-Mauer-des-Fosses, Paris, France 94100. US Agent for counsel, Wayne H. Matleski, Esq., of law firm Arent Fox Kinter Plotkin & Kahn, 1050 Connecticut Ave, Washington, DC 20036-5339, tel 202-857-6340.

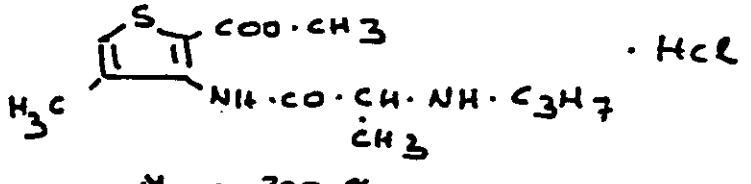
DRUG PRODUCT NAME(S):
Proprietary: Septanest
Nonproprietary/USAN: Articaine HCl (40 mg/ml) with Epinephrine bitartrate

Equivalent to 5 and 10 mcg/ml Epinephrine base.
Code Name/#: CAS# 23964-57-0
Chem Type/Ther.Class: 1 S

PHARMACOL CATEGORY/INDICATION: Infiltration anesthesia and nerve block anesthesia in clinical dentistry

DOSAGE FORM(S): Carpule; glass, 1 cartridge containing local anesthetic solution; cartridge is designed to fit in a special syringe for hypodermic injection; SVT; 1.7 ml fill;

ROUTE/ADMIN: **Parental**
DISPENSED: X **Rx** __ **OTC**
CHEMICAL NAME/STRUCTURAL FORMULA/EMPIRICAL FORMULA/MOLECULAR WEIGHT:



Mw: 320.8, ARTICAINE HCl.

Articaine is 4-methyl-3-(2-(propylamino)-propionamido)-2-thiophene carboxylic acid, methyl ester hydrochloride. Articaine has a center of asymmetry, pKa of 7.9, and it exists in solid sate in 2 polymorphic forms with melting points 170°C and 105°C.

See USP 23 page 595 for Epinephrine bitartrate.

RELATED DOCUMENTS:

DMF [redacted] DMF [redacted] is now adequate, as per review dated 4 Dec 98.

DMF [redacted] DMF [redacted] was found to be adequate (OGD/HFD-630/Karen Bernard's review dated 2.25.1993).

CONSULTS: The following consults were initiated. Micro and methods validation at HFD-926 and [redacted] on 6.15.98. and EERs on 5.13.98.

REMARKS/COMMENTS:

All manufacturing sites are acceptable to OC, including [redacted] site for Articaine, as per EES.

[redacted] has completed the methods validation work using the methods and samples provided. No major problems were encountered. A few comments made are enclosed for transmission to the firm.

Correspondence dated 2.8.99, a reiteration of issues relating to overage for epinephrine, and no new CMC information to review. Reiteration of literature citations, with no new CMC data, consisted of several attachments.

(1) Attachment A: Epinephrine concentrations, before [redacted] for 20 lots of Articaine injection drug product, to show a mean loss of about 5%.
(2) Attachment B: Minutes of teleconference dated 18th Dec 98, wherein I was absent.
(3) Attachments C to E: Publications relating to oxidative degradation of Epinephrine. Trace amounts of aluminum, 2 PPM, have shortened the shelf life to about [redacted] months. Epinephrine oxidation is complex, and it is difficult to establish a mass balance Initial rate of epinephrine loss is a function of dissolved oxygen concentration and epinephrine concentration.
(4) Attachment F: An affidavit that epinephrine degradation products in local anesthetic formulations do not pose a safety risk, by [redacted], toxicologist.
(5) Attachments G to H: Published pre-clinical toxicological data for adrenochrome and melanin, oxidative decomposition products of epinephrine.

(6) Attachment I: A publication wherein aged solutions and fresh solutions of local anesthetics with epinephrine were compared for infiltration anesthetic activity in guinea pig and SC toxicity in the mouse.

Sponsor believes that 15% epinephrine overage is justified, and the sponsor is willing to revise epinephrine overage to [redacted]%. Sponsor re-requests an extension of expiry date from [redacted] to [redacted] months.

Correspondence dated 2.5.99, a notification of intent to file an amendment with a partial response addressing issues relating to overage for epinephrine.

Correspondence dated 1.7.99, a copy of letter from USAN dated 30th Sept 98, to inform US adopted name as Articaine hydrochloride and code designation HOE 045.

Correspondence dated 12.8.98, proposed new proprietary names, Septanest [redacted]

CONCLUSIONS/RECOMMENDATIONS:

Correspondences dated 2.8.99, 2.5.99, 1.7.99 and 12.8.98, are incorrectly listed without IC code for chemistry review. All manufacturing sites are acceptable to OC, including [redacted] site for Articaine, as per EES.

Recommendations are unchanged from 29th January 99, action letter. I have seen only partial response to action items listed in approvable letter dated 29 January 99. Septonest [redacted] supplied in glass cartridges with [redacted], have [redacted] months expiry date. Either [redacted] supplies [redacted]

A note to CSO: Include a standard methods validation paragraph in the letter to the firm. Comments from [redacted], are enclosed for transmission to the firm. No major problems were encountered in the analysis of Septanest [redacted] by the firm's QC methods at [redacted]

/S/ 14.19.99
P.Maturu, PhD, Primary Review Chemist

/S/ 7/4/99
A.D'Sa, PhD, Chemistry Team Leader

cc:
Orig. NDA 20971
HFD-170/Division File
HFD-170/PMaturu, AD'Sa, JGIBBS
R/D Init. by
File name: N20971r3.99
ADEQUATE

Redacted 1

pages of trade secret and/or confidential commercial information

DIV. OF ANESTHETIC CRITICAL CARE & ADDICTION DRUG PRODUCTS
(HFD-170)

DATA SUMMARY SHEET

NDA#: 20-971 REVIEW # 2 REVIEW COMPLETION DATE: 12.8..98
PDUFA goal date is 30 Jan 99

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE
Amendment	29 Apr 98	29 Apr 98
Copies of patents and foreign package inserts for Septanest.		
Amendment	26 May 98	26 May 98
Copy of Canadian package inserts for Septanest.		
Amendment	10 Sept 98	10 Sept 98
Response to information request letter dated 19 Aug 98.		
Amendment	20 Oct 98	20 Oct 98
Copies of the correspondence with FDA labs.		
Amendment	23 Oct 98	23 Oct 98
[redacted] as an alternate supplier for [redacted]		
Amendment	1 Dec 98	1 Dec 98
[redacted] as an alternate supplier for [redacted]		

APPLICANT & ADDRESS OF APPLICANT:
Specilaities Septodont, 58 Rue Du Pont de Creteil, 94107 Saint-Mauer-des-Fosses, Paris, France 94100.

US Agent for counsel, Wayne H. Matleski, Esq., of law firm Arent Fox Kinter Plotkin & Kahn, 1050 Connecticut Ave, Washington, DC 20036-5339, tel 202-857-6340.

DRUG PRODUCT NAME(S):
Proprietary: Septanest [redacted]
Nonproprietary/USAN: Articaine HCl (40 mg/ml) with Epinephrine bitartrate

Equivalent to 5 and 10 mcg/ml Epinephrine base.
Code Name/#: CAS# 23964-57-0
Chem Type/Ther.Class: 1 S

PHARMACOL CATEGORY/INDICATION:Infiltration anesthesia and nerve block anesthesia in clinical dentistry

DOSAGE FORM(S): Carpule; glass, [redacted] cartridge containing local anesthetic solution; cartridge is designed to fit in a special syringe for hypodermic injection; SVT; 1.7 ml fill; [redacted]

ROUTE/ADMIN: Parental
DISPENSED: X Rx __ OTC

CHEMICAL NAME/STRUCTURAL FORMULA/EMPIRICAL FORMULA/MOLECULAR WEIGHT:

Articaine is 4-methyl-3-(2-(propylamino)-propionamido)-2-thiophene carboxylic acid, methyl ester hydrochloride. Articaine has a center of asymmetry, pKa of 7.9, and it exists in solid sate in 2 polymorphic forms with melting points 170 C and 105 C.

See USP 23 page 595 for Epinephrine bitartrate.

RELATED DOCUMENTS:

1) DMF — [redacted] DMF — is now adequate, as per review dated 4 Dec 98.

2) DMF — [redacted]

DMF — was found to be adequate (OGD/HFD-630/Karen Bernard's review dated 2.25.1993).

CONSULTS: The following consults were initiated. Micro and methods validation at HFD-926 and — on 6.15.98. and EERs on 5.13.98.

REMARKS/COMMENTS:

Amendment 29 April 98

German patent 1643325, on 3-aminoacylaminothiophenes and process for their manufacture assigned to Hoechst, was submitted as a reference for CMC section for Articaine HCl. Articaine, 3-n-propylamino-alpha-propylamino-2-carbometoxy-4-methylthiophene hydrochloride, was included in the comparison of relative toxicity, relative infiltration anesthesia, relative conduction anesthesia. Hostacaine was used as a reference local anesthetic. Hostacaine is not a thiophene derivative.

Amendment 10 Sept 98

Adequate response was submitted for the information request items and recommends approval of [redacted]— months expiry date request for the formulation compounded with 15% epinephrine excess. Satisfactory — months stability at [redacted] storage was submitted as an update for Septanest sterile solutions (6 lots total). Enantiomeric excess issue for Articaine was responded with the inclusion of a test for specific rotation with limts of - [redacted] degrees.

Q.1. Please provide a linkage table that correlates the following: a) clinical protocol number b) Septanest drug product lot, and c) Articaine HCl drug substance lot

R.1. Articaine HCl lot 96444 was compounded as Septanest drug product lot RD V/4A, and used as the clinical material for studies conducted under protocol numbers 96001 and 96002.

Q.2 Please provide COAs and executed batch records for the clinical materials used in Phase III Pivotal clinical study numbers are S96001US (n=569), S96002 (n=155), and S96001UK (n=158).

R.2 Submitted pages 11 to 32 include executed batch record and COA for Septanest lot RD V/4A. This [redacted] lot was mfg on 12.12.96 and the bulk was filled into glass cartridges and sealed with [redacted].

Q.3. We recommend specifications for entiomeric excess, water content and bioburden for Articiane HCl drug substance.

R.3. Included a test for [redacted] The applicant insists on [redacted] test. The applicant has provided bioburden test results for 3 lots at time zero and at [redacted] months retest point to show no significant increase in count.

Q.4. Please provide an updated stability report with the [redacted] months stability data. Please submit chromatograms at zero and [redacted] months test point.

R.4. Submitted pages 34 to 112 with chromatograms and satisfactory stability update results for the 6 test lots [redacted]

Q.5. Overage for any product merely to extend the expiration dating is not acceptable. Therefore, please provide process validation documentation that justifies use of 15% overage for Epinephrine bitartrate.

R.5. Justification was based on the following inputs, a) 15% overage for epinephrine was used in the preparation of clinical test material for Phase III studies, b) [redacted]% manufacturing loss for epinephrine for 10 test lots, c) USP monographs for epinephrine drug products have limts of 90 to 115%.

Q.6. Please submit container labels with the distributor name imprint so as to comply with 21 CFR 201.1.

R.6. Submitted page 114 with the revised cartridge label. Revised label has US distributor name (Septoodne Inc, New Castle, Delaware 19720) and mfg name (Specialites Septodont, France).

Amendments, 23 Oct 98 and 1 Dec 98

Submitted satisfactory stability test results for — months at ——— storage condition for 6 lots of Septanest (at pH 5.3) packaged with seals from ——, as a justification for the alternate supplier request. Degradation products were not monitored. Elution test results were submitted for —— seals (———— —— to show compliance with USP standards for elastomeric closures for injection. ————

———— Safety studies, such as, systemic injection test, intracutaneous test, were conducted using ———— 23 Oct 98/pages 18-20).

CONCLUSIONS/RECOMMENDATIONS:

Recommends approval of Septonest supplied in glass cartridges with ——— —— and — with — months expiry date. Seals are supplied by either—— or ———

/S/

P.Maturu, PhD, Primary Review Chemist

/S/ for Dr. D'Sa

A.D'Sa, PhD, Chemistry Team Leader 1/20/99.

cc:
Orig. NDA 20971
HFD-170/Division File
HFD-170/PMaturu, AD'Sa, JGIBBS, KNolan
R/D Init. by
File name: N20971r2
ADEQUATE

Page 5 of 11 - Addendum to chem Rev # 2 dated 12.8.98 Expiry date to —— on.
Page 6 of 11 - comments of Abi D'Sa dated 12.26.98.
Page 7 of 11 - EES Status for 3 Mfg. Sites.
Page 8 of 11 - E-mail messages between Abi D'Sa and Frank Holcombe on Epinephrine Overage and Expiry Dating.

AUG 5 1998

DIV. OF ANESTHETIC CRITICAL CARE & ADDICTION DRUG PRODUCTS
(HFD-170)

DATA SUMMARY SHEET

NDA#: 20-971 REVIEW # 1 REVIEW COMPLETION DATE: 7.15.98
Division goal date is 14 Sept 98 and PDUFA goal date is 30 Jan 99

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	3.30.98	3.30.98	4.7.98

APPLICANT & ADDRESS OF APPLICANT:
Specilaities Septodont, 58 Rue Du Pont de Creteil, 94107 Saint-Mauer-des-Fosses, Paris, France 94100.

US Agent for counsel, Wayne H. Matleski, Esq., of law firm Arent Fox Kinter Plotkin & Kahn, 1050 Connecticut Ave, Washington, DC 20036-5339, tel 202-857-6340. Sponsor's US DISTRIBUTOR is Deproco Inc, 245-C Quigley Blvd, New Castle, DE 19720, tel 302-328-5653.

DRUG PRODUCT NAME(S):
Proprietary: Septanest [redacted]

Nonproprietary/USAN: Articaine HCl (40 mg per ml) with Epinephrine bitartrate 5 and 10 mcg/ml Epinephrine base.

Code Name/#: CAS# 23964-57-0

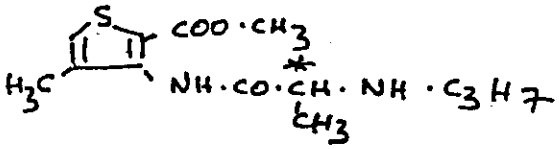
Chem Type/Ther.Class: 1 S

PHARMACOL CATEGORY/INDICATION: Infiltration anesthesia and nerve block anesthesia in clinical dentistry

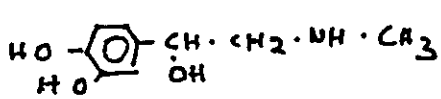
DOSAGE FORM(S): Carpule; glass, [redacted] cartridge containing local anesthetic solution; cartridge is designed to fit in a special syringe for hypodermic injection; SVT; 1.7 ml fill;

ROUTE/ADMIN: Parenteral
DISPENSED: X Rx _____ OTC
CHEMICAL NAME/STRUCTURAL FORMULA/EMPIRICAL FORMULA/MOLECULAR WEIGHT:
Articaine is 4-methyl-3-(2-(propylamino)-propionamido)-2-thiophene carboxylic acid, methyl ester hydrochloride. Articaine has a center of asymmetry, pKa of 7.9, and it exists in solid sate in 2 polymorphic forms with melting points 170 C and 105 C.

See USP 23 page 595 for Epinephrine bitartrate.



ARTICAINE (CARTICAINE)
* CENTER OF ASYMMETRY.



EPINEPHRINE

RELATED DOCUMENTS:

1) DMF [redacted]
DMF [redacted] is inadequate (my review dated 6.10.98), and information is requested.

2) DMF [redacted]
[redacted] DMF [redacted] was found to be adequate (OGD/HFD-630/Karen Bernard's review dated 2.25.1993).

CONSULTS: The following consults were initiated. Micro and methods validation at HFD-926 and [redacted] on 6.15.98. and EERs on 5.13.98.

REMARKS/COMMENTS: Adequate information was submitted to support

To support [redacted] months expiry date request, 15% epinephrine excess is used (vol 1.5 pages 195 and 196). Satisfactory [redacted] months stability at [redacted] storage was submitted for Septanest [redacted] and Septanest [redacted] sterile solutions (6 lots total). Enantiomeric excess issue for Articaine is not addressed in the submission.

Linkage table for pivotal clinical study protocol number to Septanest lots to Articaine HCl drug substance lots, COAs and executed batch records were not submitted to the NDA file. Phase III Pivotal clinical study numbers are S96001US (n=569), S96002 (n=155), and S96001UK (n=158).

The applicant has submitted a copy of the recommendation letter for CGMP compliance from Mr. Edwin Melendez, Office of compliance to Mr. Jacques Barriere, Specialites Septodont-France (vol 1 page 4). The inspectional outcome is for an inspection of [redacted] around February 1997. However, inspectional report along with the exhibits were not submitted to the file.

Certification for lack of patent infringement for Septanest drug products for the intended use was signed by Mr. David Halimi, President, Deproco Inc-USA, a sole distributor of Specialites Septodont-France (vol 1 page 47)

APPEARS THIS WAY
ON ORIGINAL

CONCLUSIONS/RECOMMENDATIONS:

Please respond to the following information items regarding Septonest — drug products manufactured at the site with CFN# 9610964 so as to complete our review of the CMC section for NDA 20971.

1) Please provide a linkage table that links the following: a) clinical study protocol number, b) Septanest drug product lot, and c) Articaine HCl drug substance lots.

2) Provide certificates of analysis and executed batch records for the clinical materials used in Phase III Pivotal clinical studies S96001US (n=569), S96002 (n=155), and S96001UK (n=158).

3) We recommend specifications for enantiomeric excess, water content and bioburden for Articaine HCL drug substance.

5) Please update stability report with the — months stability data. Please submit chromatograms at — and — months test points.

6) Overage for any product merely to extend the expiration dating is discouraged. Therefore please provide process validation documentation and a justification for the use of 15% overage for Epinephrine bitartrate.

7) Please submit container labels with the distributor name imprint so as to comply with 21 CFR 201.1

/S/

P.Maturu, PhD, Primary Review Chemist

/S/ 8/5/98

A.D'Sa, PhD, Chemistry Team Leader

cc:
Orig. NDA 20971
HFD-170/Division File
HFD-170/PMaturu, AD'Sa, JGIBBS, KNolan
R/D Init. by
File name: N20971.986
INFORMATION REQUEST

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secret and/or

confidential

commercial

information

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: **NDA 20971/000**
Priority: **14S** Org Code: **170**
Stamp: **30-MAR-1998** Regulatory Due: **03-APR-2000**
Action Goal: District Goal: **11-NOV-1998**
Applicant: **DEPROCO**
245-C QUIGLEY BLVD
NEWCASTLE, DE 19720
Brand Name: **SEPTANEST** [redacted] **(ARTICAINE HCL 4**
Established Name:
Generic Name: **ARTICAINE HCL 4%/EPINEPHINE 1/100,000/1/**
Dosage Form: [redacted]
Strength: [redacted]

FDA Contacts:

K. NOLAN	**(HF-50)**	**301-827-3376**	**, Project Manager**
P. MATURU	**(HFD-170)**	**301-827-7434**	**, Review Chemist**
A. D SA	**(HFD-170)**	**301-827-7443**	**, Team Leader**

Overall Recommendation:

ACCEPTABLE on 22-FEB-2000 by J. D AMBROGIO (HFD-324) 301-827-0062
ACCEPTABLE on 04-FEB-1999 by M. EGAS (HFD-322) 301-594-0095

Establishment: [redacted]
DMF No: [redacted]
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **22-FEB-2000**
Decision: **ACCEPTABLE**
Reason: **BASED ON FILE REVIEW**
Responsibilities: [redacted]

Establishment: [redacted]
DMF No: [redacted]
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **22-FEB-2000**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**
Responsibilities: [redacted]

Establishment: **9610964**
SPECIALITES SEPTODONT
58 RUE DU PONT DE CRETEIL
ST MAUR DES FOSSES, , FR
DMF No:
AADA No:

Profile: **SVS** OAI Status: **NONE**

ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Responsibilities: **FINISHED DOSAGE MANUFACTURER**

Last Milestone: **OC RECOMMENDATION**
Milestone Date **22-FEB-2000**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Redacted 14

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confidential

commercial

information