CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
20-971

Approval Letter

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NDA 20-971

Deproco, Inc.
c/o Arent Fox Kintner Plotkin & Kahn, PLLC
1050 Connecticut Avenue, N.W.
Washington, DC 20036-5339

APR 0 3 2000

Attention: Wayne Matelski, Esq.

Dear Mr. Matelski:

Please refer to the new drug application (NDA) dated March 30, 1998, received March 30, 1998, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Septocaine™ (articaine hydrochloride 4% with epinephrine 1:100,000 for injection).

We also refer to your amendments dated April 29, May 18 and 26, August 21, September 10, October 23, and December 1, 1998, March 9 and May 4, 1999, and February 3, 24, and 28 and March 16, 2000. Your submission of February 3, 2000, constituted a complete response to our May 7, 1999, action letter.

This new drug application provides for the use of Septocaine™ for local, infiltrative, or conductive anesthesia in both simple and complex dental and periodontal procedures.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon enclosed labeling text. As agreed, 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. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert) and the immediate container and carton labels submitted March 31, 2000, with the change listed above. Marketing the product with FPL that is not identical to the approved labeling may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 20-971." Approval of this submission by FDA is not required before the labeling is used.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

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

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Laura Governale, Pharm.D., Regulatory Project Manager, at (301) 827-7410.

Sincerely,

/S/

Lisa D. Rarick, M.D.
Deputy Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
20-971

Approvable Letter

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NDA 20-971

Arent Fox
1050 Connecticut Avenue, NW
Washington, D.C. 20036-5339

MAY 7 1999

Attention: Wayne H. Matelski, J.D.
United States Agent for and Counsel to
Deproco, Inc. and Specialites Septodont

Dear Mr. Matelski:

Please refer to your pending March 30, 1998 New Drug Application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Septanest — (articaine hydrochloride 4% with Epinephrine 1/200,000 solution injection) and Septanest — (articaine hydrochloride 4% with Epinephrine 1/100,000 solution injection).

We acknowledge receipt of your submissions dated March 9, 1999 and May 4, 1999.

Your submission of March 9, 1999 constituted a complete response to our January 29, 1999 action letter.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following deficiencies:

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.

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 —% 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.

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).

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

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

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

2. Retabulation of drop-outs with new drop-outs identified. Discuss, if appropriate.

3. Details of any significant changes or findings.

4. Summary of worldwide experience on the safety of this drug.

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

6. English translations of any approved foreign labeling not previously submitted.

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

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up

form, not final print. Please send one copy to the Division of Anesthetic, Critical Care, and Addiction Drug Products, HFD-170 and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal or telephone conference with the Division of Anesthetic, Critical Care, and Addiction Drug Products, HFD-170 to discuss what further steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, contact Susmita Samanta, Regulatory Project Manager, at 301-827-7410.

Sincerely,

/S/ FOR 5/7/99

John K. Jenkins, M.D., F.C.C.P.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

cc:
Archival NDA 20-971
HFD-170/Div. Files
HFD-170/SS/Moody (with labeling)
HFD-170/McCormick/Rappaport/Blatt (with labeling)
HFD-170/D'Sa/Maturu (with labeling) 5/7/99
HFD-170/Jean/Goheer
HFD-170/Permutt/Klein
HFD-700/Hu
HFD-160/Uranti
HFD-44/Askine/Abrams (with labeling)
HFD-344/Thomas/Snipes
HFD-002/ORM
HFD-103/ADRA
HFD-95/DDMS
HFD-40/DDMAC (with labeling)
HFD-820/DNDC Division Director
HFD-102/Jenkins (with labeling)
HFD-102/Ripper (with labeling)
HFD-103/Raczkowski (with labeling)
DISTRICT OFFICE

Drafted by: SS/May 6, 1999
Initialed by: C.P.Moody/May 6, 1999
final:
filename:20971.M06.AE

APPROVABLE (AE)

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

Review from DFS

AE 1/29/99

NDA 20-971

Arent Fox
1050 Connecticut Avenue, NW
Washington, D.C. 20036-5339

Attention: Wayne H. Matelski, J.D.
United States Agent for and Counsel to
Deproco, Inc. and Specialities Septodont

Dear Mr. Matelski:

Please refer to your pending March 30, 1998 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Septanest — (articaine hydrochloride 4% with Epinephrine 1/200,000 solution injection) and Septanest — (articaine hydrochloride 4% with Epinephrine 1/100,000 solution injection).

We acknowledge receipt of your submissions dated April 29, 1998, May 18, 1998, May 26, 1998, August 21, 1998, September 10, 1998, October 23, 1998, December 1, 1998, and December 4, 1998.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following:

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

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

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

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

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

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

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

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

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

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

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

2. Retabulation of drop-outs with new drop-outs identified. Discuss, if appropriate.

3. Details of any significant changes or findings.

4. Summary of worldwide experience on the safety of this drug.

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

6. English translations of any approved foreign labeling not previously submitted.

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

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

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal or telephone conference with the Division of Anesthetic, Critical Care, and Addiction Drug Products, HFD-170 to discuss what further steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, contact Ken Nolan, Project Manager, at (301) 827-7410.

Sincerely,
/S/

Victor Raczkowski, M.D.
Acting Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
Archival NDA 20-971
HFD-170/Div. Files
HFD-170/KEN/Moody
HFD-170/McCormick/Rappaport/Blatt
HFD-170/D'Sa/Maturu
HFD-170/Jean/Goheer
HFD-170/Permutt/Klein
HFD-700/Hu
HFD-160/Uranti
HFD-44/Askine/Abrams
HFD-344/Thomas/Snipes
HFD-002/ORM
HFD-103/ADRA
HFD-95/DDMS
HFD-40/DDMAC (with labeling)
HFD-820/DNDC Division Director
DISTRICT OFFICE

Drafted by: KEN/November 10, 1998\Rev.\November 13, 1998\\Rev.1-15-99\KEN\\Rev. 1-15-99\Moody-ken\\Rev.\\1-20-99\Theodorakis-ken\\Rev.1-26-99\Collier-ken\\Rev.1-27-99\Theodorakis-ken\\Rev.1-27-99\Moody-ken\\Rev.\1-28-99\D'Sa-ken
Initialed by:
final:
filename: n:\cso\nolan\N20971AE.110

APPROVABLE (AE)

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