CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-027

ADMINISTRATIVE DOCUMENTS

LAW OFFICES
STROUD, STROUD, WILLINK, THOMPSON & HOWARD
25 WEST MAIN STREET
P.O. BOX 2236
MADISON, WISCONSIN 53701-2236

TELEPHONE (608) 257-2281
FACSIMILE (608) 257-7643

E. VERNON HOWARD
DONALD W. TODD
ROBERT R. STROUD
M. DALE PETERSON
ROBERT J. SCHWAB
CAROLYN A. HEGGE
JAMES F. GEBHART*
TERESA J. WELCH
BRADY J. FRENCHICK†
GEORGE F. VENCI JR.*
MARGARET M. LISS
JOSEPH P. BARTOL
PIERRE DAVID ROANG*
KAREN B. KING

RAY N. STROUD
(1910-1972)

SEWARD R. STROUD
DONALD R. STROUD
DONALD D. WILLINK
DALE R. THOMPSON
CARL E. GULBRANDSEN
OF COUNSEL

*ALSO ADMITTED IN ILLINOIS
†ALSO ADMITTED IN MINNESOTA

PATENT INFORMATION
under 21 C.F.R. §314.53

Patent	Expiration Date	Type of Patent	Patent Owner
Patent No. 3,907,843	September 23, 1992	drug	Wisconsin Alumni Research Foundation
Patent No. 5,602,116	April 3, 2115	method of use	Bone Care International, Inc.
Patent No. 5,707,980	February 11, 2117	method of use	Bone Care International, Inc.

PATENT DECLARATION

The undersigned declares that Patent Nos. 5,602,116 and 5,707,980 cover the formulation, composition and/or method of use of 1α-D_2. This product is the subject of this application for which approval is being sought.

Teresa J. Welch, Ph.D.
Patent Attorney for Applicant

APPEARS THIS WAY
ON ORIGINAL

LAW OFFICES
STROUD, STROUD, WILLINK, THOMPSON & HOWARD
25 WEST MAIN STREET
P.O. BOX 2236
MADISON, WISCONSIN 53701-2236

TELEPHONE (608) 257-2281
FACSIMILE (608) 257-7643

VERNON HOWARD
DONALD W. TODD
ROBERT R. STROUD
M. DALE PETERSON
ROBERT J. SCHWAB
CAROLYN A. HEGGE
JAMES F. GEBHART*
TERESA J. WELCH
GRADY J. FRENCHICK†
GEORGE F. VENCI JR.*
MARGARET M. LISS
JOSEPH P. BARTOL
SVERRE DAVID ROANG*
KAREN B. KING

RAY M. STROUD
(1910-1972)

SEWARD R. STROUD
DONALD R. STROUD
DONALD D. WILLINK
DALE R. THOMPSON
CARL E. GULBRANDSEN
OF COUNSEL

*ALSO ADMITTED IN ILLINOIS
†ALSO ADMITTED IN MINNESOTA

PATENT CERTIFICATION
under 21 C.F.R. §314.50(i)

PARAGRAPH II CERTIFICATION

U.S. Patent No. 3,907,843

In its opinion and to the best of its knowledge of Bone Care International, Inc., Bone Care International, Inc. certifies that Patent No. 3,907,843 which claims 1a-D_2 for which this application is submitted, expired on September 23, 1992.

Teresa J. Welch, Ph.D.
Patent Attorney for Applicant

APPEARS THIS WAY
ON ORIGINAL

LAW OFFICES
STROUD, STROUD, WILLINK, THOMPSON & HOWARD
25 WEST MAIN STREET
P.O. BOX 2236
MADISON, WISCONSIN 53701-2236

TELEPHONE (608) 257-2281
FACSIMILE (608) 257-7643

VERNON HOWARD
DONALD W. TODD
ROBERT R. STROUD
H. DALE PETERSON
ROBERT J. SCHWAB
CAROLYN A. HEGGE
JAMES F. GEBHART*
TERESA J. WELCH
BRADY J. FRENCHICK†
MARGARET M. LISS
JOSEPH P. BARTOL
EVERRE DAVID ROANG*
KAREN B. KING

RAY H. STROUD
(1910-1972)

SEWARD R. STROUD
DONALD R. STROUD
DONALD D. WILLINK
DALE R. THOMPSON
CARL E. GULBRANDSEN
OF COUNSEL

*ALSO ADMITTED IN ILLINOIS
†ALSO ADMITTED IN MINNESOTA

PARAGRAPH III CERTIFICATION

U.S. Patent No. 5,602,116

In its opinion and to the best of its knowledge of Bone Care International, Inc., Bone Care International, Inc. certifies that Patent No. 5,602,116 will expire on April 3, 2115.

Teresa J. Welch, Ph.D.
Patent Attorney for Applicant

U.S. Patent No. 5,707,980

In its opinion and to the best of its knowledge of Bone Care International, Inc., Bone Care International, Inc. certifies that Patent No. 5,602,116 will expire on February 11, 2117.

Teresa J. Welch, Ph.D.
Patent Attorney for Applicant

APPEARS THIS WAY
ON ORIGINAL

LAW OFFICES

STROUD, STROUD, WILLINK, THOMPSON & HOWARD

25 WEST MAIN STREET

P.O. BOX 2236

MADISON, WISCONSIN 53701-2236

TELEPHONE (608) 257-2281

FACSIMILE (608) 257-7643

C. VERNON HOWARD
RONALD W. TODD
ROBERT R. STROUD
N. DALE PETERSON
ROBERT J. SCHWAB
CAROLYN A. HEGGE
JAMES F. GEBHART*
TERESA J. WELCH
BRADY J. FRENCHICK†
GEORGE F. VENCI JR.*
MARGARET M. LISS
JOSEPH P. BARTOL
SVERRE DAVID ROANG*
KAREN B. KING

RAY H. STROUD
(1910-1972)

SEWARD R. STROUD
DONALD R. STROUD
DONALD D. WILLINK
DALE R. THOMPSON
CARL E. GULBRANDSEN
OF COUNSEL

*ALSO ADMITTED IN ILLINOIS
†ALSO ADMITTED IN MINNESOTA

METHOD OF USE PATENT CERTIFICATION

In its opinion and to the best of its knowledge of Bone Care International, Inc., Bone Care International, Inc. certifies that Patent Nos 5,602,116 and 5,707,980 claim as a method of use the indication of the drug product for which applicant is seeking approval.

Teresa J. Welch, Ph.D.
Patent Attorney for Applicant

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved; OMB No. 0910-0396
Expiration Date: 3/31/02

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

☒ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		
	See attached list.	

☐ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Dale W. Gutman	Vice President - Finance
FIRM/ORGANIZATION	
Bone Care International, Inc.	
SIGNATURE	**DATE**
Dale W. Gutman	5/10/99

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

FORM FDA 3454 (3/99)

Investigators for Study No. H-114
NDA No. 21-027

Acchiardo, S., M.D.

Bower, J.D., M.D.

Chesney, R.W., M.D.

Coburn, J.W., M.D.

Frazao, J., M.D.

Gallagher, J.C., M.D.

Goodman, W.G., M.D.

Hernandez, J., M.D.

Kelley, B.J., M.D.

Levine, B.S., M.D.

Norris K., M.D.

Robertson, J.A., M.D.

Rodriguez, H.J., M.D.

Rutkowski, M., M.D.

Sigala, J., M.D.

Exclusivity Checklist

NDA:	21-027
Trade Name:	Hectorol Injection
Generic Name:	doxercalciferol
Applicant Name:	Bone Care International
Division:	DMEDP
Project Manager:	/S/
Approval Date:	

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a. Is it an original NDA?	Yes	X	No	
b. Is it an effectiveness supplement?	Yes		No	X
c. If yes, what type? (SE1, SE2, etc.)				
Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")	Yes	X	No	

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

Explanation:

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

Explanation:

d. Did the applicant request exclusivity?	Yes		No	X
If the answer to (d) is "yes," how many years of exclusivity did the applicant request?				

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?	Yes		No	X
If yes, NDA #				
Drug Name:				

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS.				
3. Is this drug product or indication a DESI upgrade?	Yes		No	X
IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS (even if a study was required for the upgrade).				

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.	Yes	X	No	
Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.	Yes	X	No	

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

Drug Product	Hectoral Caps.
NDA #	20-562
Drug Product	
NDA #	
Drug Product	
NDA #	

2. Combination product.	Yes		No	
If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing <u>any one</u> of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)	Yes		No	

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

Drug Product	
NDA #	
Drug Product	
NDA #	
Drug Product	

NDA #				
IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS. IF "YES," GO TO PART III.				
PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS				
To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."				
1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.	Yes	X	No	
IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS.				
2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application. For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.				
a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?	Yes	X	No	
If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCKS.**				
Basis for conclusion:				
b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?	Yes		No	X
1) If the answer to 2 b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.	Yes		No	

If yes, explain:				
2) If the answer to 2 b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?	Yes		No	X
If yes, explain:				
c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:				
Investigation #1, Study #:	H-114			
Investigation #2, Study #:				
Investigation #3, Study #:				
3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.				
a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")				
Investigation #1	Yes		No	X
Investigation #2	Yes		No	
Investigation #3	Yes		No	
If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:				
Investigation #1 -- NDA Number				
Investigation #2 -- NDA Number				
Investigation #3 -- NDA Number				
b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?				
Investigation #1	Yes		No	X
Investigation #2	Yes		No	
Investigation #3	Yes		No	
If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:				
Investigation #1 -- NDA Number				
Investigation #2 -- NDA Number				
Investigation #3 -- NDA Number				
If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the				

application or supplement that is essential to the approval (i.e., the investigations listed in #2 (c), less any that are not "new"):

Investigation #1	
Investigation #2	
Investigation #3	

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a. For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1	Yes	X	No	
IND#:				
Explain:				
Investigation #2	Yes		No	
IND#:				
Explain:				
Investigation #3	Yes		No	
IND#:				
Explain:				

b. For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	Yes		No	
IND#:				
Explain:				
Investigation #2	Yes		No	
IND#:				
Explain:				
Investigation #3	Yes		No	
IND#:				
Explain:				

c. Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)	Yes		No	X
If yes, explain:				

BACK TO TOP

Signature of PM/CSO /S/

Date: 3/16/00

Signature of Division Director /S/

Date: 4/5/00

cc:
Original NDA
Division File
HFD-93 Mary Ann Holovac

BACK TO TOP

APPEARS THIS WAY
ON ORIGINAL

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	21027	**Trade Name:**	HECTOROL (DOXERCALCIFEROL)2.0MCG/ML INJ
Supplement Number:		**Generic Name:**	DOXERCALCIFEROL
Supplement Type:		**Dosage Form:**	Injectable; Injection
Regulatory Action:	AP	**Proposed Indication:**	Hectorol is indicated in the management of secondary hyperparathyroidism in patients undergoing chronic renal dialysis.

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

NO, No data was submitted for this indication

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days)
____Infants (1-24 Months)
X Other Age Groups (listed): 17-20
X Children (25 months-12 Years)
X Adolescents (13-16 Years)

Label Adequacy	Inadequate for ALL pediatric age groups
Formulation Status	NO NEW FORMULATION is needed
Studies Needed	STUDIES needed.
Study Status	

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

COMMENTS:

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

/S/

Signature

3/17/00

Date

Bone Care
INTERNATIONAL

One Science Court Madison, WI 53711 Phone: (608) 236-2500 Fax: (608) 236-0314

Debarment Certification

Bone Care International certifies that it did not or will not use in any capacity the services of any person debarred under subsection (a) or (b) [section 306(a) or (b)], in connection with this application [Section 306(k)(1) of the GDEA (21 U.S.C. 335a(k)(1).]

Darlene M. Kyllo, RAC
Director, Quality, Compliance, and Regulatory Affairs

January 29, 1999
Date

APPEARS THIS WAY
ON ORIGINAL

NDA 21-027
Hextorol (docercalciferol) Injection
Bone Care International

The clinical trial for the IV formulation was done at the same sites as the capsule formulation that was approved June 9, 1999. Therefore, no sites were requested to be audited.

Division Director Memo
New Drug Application

NDA: 21-027

Sponsor: Bone Care International.

Drug: Hectorol™ (doxercalciferol) Injection

Indication: Reduction of elevated iPTH levels in the management of secondary hyperparathyroidism in patients undergoing chronic renal dialysis

Date received: February 2, 1999

Date of Memo: April 6, 2000

Medical and Regulatory Background

Doxercalciferol is a synthetic vitamin D analog that undergoes metabolic activation *in vivo* to form 1α, 25-dihydroxyvitamin D_2, a naturally occurring, biologically active form of vitamin D_2. Vitamin D levels in humans depend on exposure to ultraviolet rays for conversion of 7-dehydrocholesterol in the skin to vitamin D_3 and dietary intake of either vitamin D_2 or vitamin D_3. Both forms, vitamins D_2 and D_3, must be metabolically activated in the liver and kidney before becoming fully active on target tissues.

The metabolically active forms of vitamin D regulate blood calcium at levels required for essential body functions. Specifically, the biologically active vitamin D metabolites control the intestinal absorption of dietary calcium, the tubular reabsorption of calcium by the kidney and, in conjunction with parathyroid hormone (PTH), the mobilization of calcium from the skeleton. They act directly on osteoblasts to stimulate skeletal growth, and on the parathyroid glands to suppress PTH synthesis and secretion. In patients with end-stage renal disease (ESRD), deficient production of biologically active vitamin D metabolites leads to low calcium levels. This low calcium level stimulates the parathyroid gland to supply excessive amounts of PTH. Excessive PTH then results in over-mobilization of calcium from the skeleton producing bone disease (renal osteodystrophy) in these patients.

In ESRD, there is no impairment of 25 hydroxylation (as this takes place in the liver, not the kidney) and doxercalciferol is rapidly hydroxylated to form the active form of vitamin D. Hectorol (doxercalciferol) as an oral formulation has been reviewed and was approved for use in the management of secondary hyperparathyroidism in patients with ESRD in June, 1999 through NDA 20-862, submitted by Bone Care International. To establish clinical effectiveness and to demonstrate appropriate safety of the oral formulation, the applicant submitted results from two, identically designed, phase 3 studies. These studies were designed to demonstrate the effect of Hectorol in suppressing parathyroid secretion.

Subjects underwent an eight-week washout period (to eliminate the effect of previous treatment with vitamin D active substances) and were then treated with Hectorol for 16 weeks where the dose was titrated to pharmacodynamic effect. After this open period of treatment, there followed an 8-week double-blind period in which patients were randomized (the actual randomization scheme was applied at the beginning of the washout period) to either continued Hectorol treatment or placebo. The results of the double-blind period confirmed a significant decrease from baseline (the last three weeks of the washout period) of intact PTH (iPTH) levels in the Hectorol group and a small, non-significant decrease in the iPTH level (compared to baseline) in the placebo group.

During the review of the oral doxercalciferol application, this application for the intravenous formulation, NDA 21-027, was received (February 2). This application underwent a preliminary review during the initial 60-day filing period and the applicant was informed that the application would not be filed. The regulatory letter describing this "refusal to file" (RTF) was dated April 1, 1999. The RTF was based on a determination that the phase 3 clinical trials performed in order to support the intravenous formulation did not have adequate controls and the application lacked necessary information on plasma drug/metabolite levels.

According to the code of federal regulations (CFR), 314.101(3), if FDA refuses to file an application, the applicant may request in writing, within 30 days of the date of the RTF letter, an informal conference with the agency about whether the agency should file the application. If, following the informal conference, the applicant requests that the FDA file the application (with or without amendments to correct the deficiencies), the agency will file the application over protest and review it as filed. When an application is filed over protest, the date of filing is the date 60 days after the date the applicant requested the conference. In the case of NDA 21-027, the sponsor requested a meeting on April 6, 1999. A meeting was held with the sponsor on April 9, 1999. Although it was not initially clear that this meeting request constituted a request to file over protest, later communications with the applicant led the division to issue a regulatory letter confirming the filing of this application over protest and resume review of this application.

Although the medical officer primary review describes his concern regarding the filing of this application and the design of the clinical studies and control groups used, the data provided are adequate for review. The complete reviews are included in the action package and are briefly described here.

Clinical/Statistical

In terms of the concern about the adequacy of the control group(s), many different possible comparative control groups are acceptable (including historical controls, comparison to baseline values, cross study comparisons, active controls, placebo controls, etc) depending on the clinical setting and scientific need. Further, as described in a May 1998 "Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products", in certain cases, "effectiveness of a new product may be adequately demonstrated without additional adequate and well-controlled clinical efficacy trials". This guidance provides, as one example, situations of extrapolation from one dosage from to another—especially where a "well-defined pharmacokinetic/pharmacodynamic relationship" exists.

In the case of Hectorol, pharmacokinetic comparison of the IV and oral formulations is not possible at this time due to a lack of a valid assay for the drug. Thus, confirmation of the pharmacodynamic effect of the IV formulation is necessary for the appropriate extrapolation of safety and effectiveness of the oral formulation.

To establish the appropriate use of the intravenous formulation, the division agreed to a study design in which subjects who had been studied in the two phase 3 trials establishing the safety and effectiveness of the oral formulation of Hectorol were enrolled in two further trials. The sponsor had originally intended to immediately crossover patients who completed the study of the oral formulation. However, due to a lack of supply of the intravenous Hectorol, this study continuation was delayed by six months. During this six-month delay, subjects received alternative forms of vitamin D. Thus, rather than an immediate crossover to the IV formulation, subjects underwent a washout period followed by 12 weeks of open-label treatment with IV Hectorol.

As presented in the medical team leader review, the pharmacodynamic effect is substantially demonstrated in the two phase 3 trials submitted. As described, the use of the washout period and comparison to baseline PTH values is a very reasonable and sound approach to confirming the pharmacological effect of IV Hectorol in ESRD. Safety parameters are also reviewed in the medical team leader memo and results confirm safety (and point toward a possible improved safety profile, although the design and comparison

do not allow for any type of superiority claim) of the IV formulation compared to results seen in the earlier studies of oral Hectorol. This review also describes the possible impact of the six-month postponement of these clinical trials and concerns of enrichment of the study population due to the design of the trials and the delayed execution of the trials.

As reflected in the statistical review and evaluation, there were many limitations to the study as designed and executed. The summary finding in this review supports that Hectorol IV produced statistically significant reductions in iPTH levels from baseline in a selected group of patients who had previously completed treatment with oral Hectorol.

The medical officer primary review also describes a concern regarding the ethnicity of the study population. As Dr. Lutwak describes, the majority of patients with ESRD are white (61%) with equal distribution between sexes. The patient population for the two study groups enrolled to support the oral and then IV formulations of Hectorol included equal numbers of males and females. The two studies included a majority of black subjects (61% in one study and 100% in the other). This difference was also described in the review for the oral formulation. In that review, the medical officer concluded that this difference in ethnic distribution was not significant. It appears that no differences in risk or benefit have been observed based on ethnicity for either formulation.

Clinical Audits

Because the clinical study sites for this application are identical to those provided in NDA 20-862 (oral doxercalciferol), and because these sites were audited and found acceptable in support of the NDA for the oral formulation, no new clinical audits were performed for NDA 21-027.

Clinical Pharmacology and Biopharmaceutics

The sponsor has not submitted new information to this NDA, but cross-referenced both oral and intravenous clinical pharmacology and biopharmaceutics information found in NDA 20-862 (oral doxercalciferol). As per the biopharmaceutics reviewer, the earlier NDA, NDA 20-862 was not found acceptable because of inadequate assay validation and lack of adequate relative bioavailability information. Because of the method of use of doxercalciferol, namely titration of dose to effect under carefully monitored clinical settings to pharmacodynamic effect, these deficiencies in pharmacokinetics information were not considered crucial to the approval of the oral formulation. The same argument applies to the current intravenous formulation.

Thus, even with the lack of assay validation and complete bioavailability information, the approval of intravenous doxercalciferol is appropriate. Similar to the oral formulation, this product is provided in a closely monitored setting (renal dialysis) and the dose is titrated to pharmacological effect.

Pharmacology/Toxicology

Adequate pharmacology/toxicity studies were submitted to NDA 20,862 (Hectorol capsules) to support approval of the oral formulation of doxercalciferol. No new studies are necessary and none were submitted in this application. The pharmacology reviewer recommends approval.

Chemistry

As per the chemistry review, appropriate chemistry and microbiology information have been submitted to support approval of doxercalciferol injection.

Labeling

Labeling comments from the various disciplines were conveyed to the sponsor. Discussion and agreement that related to these comments resulted in the draft labeling submitted on March 29, 2000. This labeling is acceptable.

Phase 4 Commitments

Several Phase 4 commitments were specified in the approval of the oral form of doxercalciferol. These included several [redacted] as well as a commitment to develop an [redacted] Although the chemistry reviewer suggests that these commitments be reiterated in this action letter, I believe that the current commitments as specified to NDA 20-862 are adequate and do not need to be restated in this letter.

Recommendations

Approval

/S/ 4/6/00

Lisa Rarick, MD
Deputy Director, Office of Drug Evaluation 2
For Acting Director, Division of Metabolic and Endocrine Drug Products

cc: NDA 21-027
HFD-510/Lutwak/Colman/Hedin
HFD-102/Jenkins

APPEARS THIS WAY
ON ORIGINAL

NDA 21-027
Hextorol (docercalciferol) Injection
Bone Care International

No pharmacology section was submitted. The label has been reviewed by Dr. Steigerwalt, and is acceptable.

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: NDA 21027/000
Stamp: 01-FEB-1999 Regulatory Due: 06-FEB-2000
Applicant: BONE CARE
1 SCIENCE CT
MADISON, WI 53711

Priority: 3S Org Code: 510
Action Goal: District Goal: 17-DEC-1999
Brand Name: HECTOROL (DOXERCALCIFEROL)2.0MCG/ML INJ
Established Name:
Generic Name: DOXERCALCIFEROL
Dosage Form: INJ (INJECTION)
Strength: 2.0 MCG/ML

FDA Contacts:

D. HEDIN	(HFD-510)	301-827-6392	, Project Manager
M. HABER	(HFD-510)	301-827-6420	, Review Chemist
D. WU	(HFD-510)	301-827-6375	, Team Leader

Overall Recommendation:

ACCEPTABLE on 29-MAR-2000 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment: [redacted]
DMF No:
AADA No:

Profile: SVS OAI Status: NONE
Last Milestone: OC-RECOMMENDATION
Milestone Date: 16-NOV-1999
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION
Responsibilities: FINISHED DOSAGE PACKAGER

Establishment: [redacted]
DMF No:
AADA No:

Profile: SVS OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 16-NOV-1999
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION
Responsibilities: FINISHED DOSAGE MANUFACTURER

Establishment: [redacted]
DMF No:
AADA No:

Profile: SVS OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Responsibilities: FINISHED DOSAGE LABELER

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Milestone Date: **29-MAR-2000**
Decision: **ACCEPTABLE**
Reason: **OBSER. NOT SIGNIFICANT ENOUG**

Establishment: **2132013**
BONE CARE INTERNATIONAL INC
1 SCIENCE CT
MADISON, WI 53711

DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **22-DEC-1999**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **DRUG SUBSTANCE STABILITY TESTER**

Establishment: [redacted]

DMF No:
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **28-OCT-1999**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: **DRUG SUBSTANCE MANUFACTURER**

APPEARS THIS WAY
ON ORIGINAL