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**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER:**

**ADMINISTRATIVE/CORRESPONDENCE DOCUMENTS**

# Bone Care

INTERNATIONAL

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

June 9, 1999

Solomon Sobel, M.D., Director  
Division of Metabolism and Endocrine Drug Products  
Food and Drug Administration  
Center for Drug Evaluation and Research (HFD-510)  
Attention: Document Control Room - 14B19  
5600 Fishers Lane  
Rockville, MD 20857

RE: NDA No. 20-862 for 1-alpha-hydroxyvitamin D<sub>2</sub> (Hectorol™)

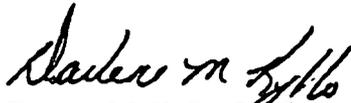
Dear Dr. Sobel:

Pursuant to my telephone conversation with Julie Rhee this afternoon, we have prepared and attached a clean copy of the revised label for Hectorol™. The revised labeling contains the following three modifications suggested by DMEDP:

1. Doxercalciferol has been changed to  $1\alpha,25-(OH)_2D_2$  under CLINICAL PHARMACOLOGY/Pharmacokinetics and Metabolism; second paragraph; sixth line.
2. The word "serum" has been deleted from the phrase "dosage titrated to achieve target serum iPTH levels" under ADVERSE REACTIONS; first paragraph; fifth line.
3. An "i" has been inserted in front of "PTH" under DOSAGE AND ADMINISTRATION; second paragraph; in both the seventh and ninth lines.

The revised labeling is being sent via fax, email, and overnight courier.

Sincerely,



Darlene M. Kyilo, RAC  
Director, Compliance, Quality, & Regulatory Affairs

Enclosure

# Bone Care

INTERNATIONAL

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

June 9, 1999

Solomon Sobel, M.D., Director  
Division of Metabolism and Endocrine Drug Products  
Food and Drug Administration  
Center for Drug Evaluation and Research (HFD-510)  
Attention: Document Control Room - 14B19  
5600 Fishers Lane  
Rockville, MD 20857

RE: NDA No. 20-862 for 1-alpha-hydroxyvitamin D<sub>2</sub> (Hectorol™)

Dear Dr. Sobel:

Pursuant to the faxed correspondence from Julie Rhee, dated June 9, 1999, we have prepared and attached a clean copy of the revised label for Hectorol™. The revised labeling contains all of the modifications suggested by DMEDP in today's fax.

In addition, the container label has been modified as requested to include the actual NDC number for the 50 count bottles.

Sincerely,



Darlene M. Kyllor, RAC  
Director, Compliance, Quality, & Regulatory Affairs

Enclosure

# Bone Care

INTERNATIONAL

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

June 8, 1999

John Jenkins, M.D., Director  
Office of Drug Evaluation II  
Food and Drug Administration  
Center for Drug Evaluation and Research (HFD-510)  
5600 Fishers Lane  
Rockville, MD 20857

RE: NDA No. 20-862 for 1-alpha-hydroxyvitamin D<sub>2</sub> (Hectorol™)

Dear Dr. Jenkins:

Pursuant to the faxed and emailed correspondence received from Julie Rhee, dated June 8, 1999, we have prepared and attached a copy of the revised labeling for Hectorol™. The revised Hectorol™ labeling contains all of the modifications requested by ODE II today with the following exceptions:

1. Under CLINICAL PHARMACOLOGY, the suggested wording is misleading in the fourth sentence: "The sequential products of this reaction are 25-(OH)D<sub>2</sub> and 25-(OH)D<sub>3</sub>." Vitamin D<sub>2</sub> is hydroxylated to 25-(OH)D<sub>2</sub> and vitamin D<sub>3</sub> is hydroxylated to 25-(OH)D<sub>3</sub>; thus we have deleted [REDACTED] and re-inserted [REDACTED]
2. We propose deleting the second table under CLINICAL PHARMACOLOGY / Clinical Studies entirely, along with the preceding paragraph, and moving the last paragraph in the section up into the paragraph under the first table. Thus, the last paragraph of this section would then read:

[REDACTED]

with placebo.

John Jenkins, M.D., Director

June 8, 1999-

Page 2

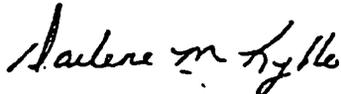
Alternatively, if you do not wish to delete the second table with its preceding paragraph, we have corrected the numeric values in the table. Further, the suggested "Hect." has been expanded to "Hectorol" and the suggested "Plac." has been expanded to "Placebo".

In addition, minor corrections have been made, and are fully illustrated by the strike-throughs and highlights.

The revised labeling is attached in Word format; the revised carton and container labels are attached in Adobe Acrobat format. This entire submission is being faxed to Julie Rhee at DMEDP, to fax number 301-443-9282.

Thank you for your timely review of this revised labeling. I can be reached by phone at 608-236-2530 or by fax at 608-236-0314.

Sincerely,



Darlene M. Kylo, RAC  
Director, Compliance, Quality, & Regulatory Affairs

Enclosure

LAW OFFICES

STROUD, STROUD, WILLINK, THOMPSON & HOWARD

25 WEST MAIN STREET

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RAY M. STROUD  
(1910-1972)

SEWARD R. STROUD  
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OF COUNSEL

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MARGARET M. LISS  
JOSEPH P. BARTOL  
SVERRE DAVID ROANG  
KAREN B. KING

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

<u>Patent</u>	<u>Expiration Date</u>	<u>Type of Patent</u>	<u>Patent Owner</u>
U.S. Patent No. 3,907,843	September 23, 1992	drug	Wisconsin Alumni Research Foundation
U.S. Patent No. 5,602,116	April 3, 2115	method of use	Bone Care International, Inc.
U.S. 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  $1\alpha$ -D<sub>2</sub>. This product is the subject of this application for which approval is being sought.



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

LAW OFFICES

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**PATENT CERTIFICATION**  
under 21 C.F.R. 5314.50(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<sub>2</sub> for which this application is submitted, expired on September 23, 1992.



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

LAW OFFICES

**STROUD, STROUD, WILLINK, THOMPSON & HOWARD**

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SVERRE DAVID ROJANG  
MAREN S. KING

**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

LAW OFFICES

**STROUD, STROUD, WILLINK, THOMPSON & HOWARD**

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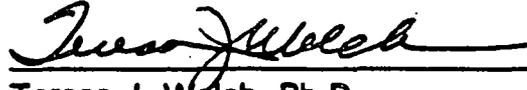
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OF COUNSEL

\*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

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EXCLUSIVITY SUMMARY FOR NDA # 20-862 SUPPL # \_\_\_\_\_

Trade Name Hectorol Generic Name doxercalciferol

Applicant Name Bayer Corp. International HFD # 510

Approval Date If Known \_\_\_\_\_

**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 question about the submission.

a) Is it an original NDA? YES /  / NO /  /

b) Is it an effectiveness supplement? YES /  / NO /  /

If yes, what type? (SE1, SE2, etc.) \_\_\_\_\_

c) 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 /  / 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.

\_\_\_\_\_  
\_\_\_\_\_

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:

\_\_\_\_\_  
\_\_\_\_\_

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d) Did the applicant request exclusivity?

YES /    /      NO /    /

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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? (Rx to OTC switches should be answered NO-please indicate as such)

YES /    /      NO /    /

If yes, NDA # \_\_\_\_\_ Drug Name \_\_\_\_\_

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /    /      NO /    /

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (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.

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

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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 / \_\_\_ /      NO /  /

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

NDA# \_\_\_\_\_  
NDA# \_\_\_\_\_  
NDA# \_\_\_\_\_

2. Combination product.

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 any one 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).

NDA# \_\_\_\_\_  
NDA# \_\_\_\_\_  
NDA# \_\_\_\_\_

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. 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 /\_\_\_/ NO /\_\_\_/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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.

(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 /\_\_\_/ NO /\_\_\_/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

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(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 /\_\_\_/

(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 /\_\_\_/

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:

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Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.



c) 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"):

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  
IND # \_\_\_\_\_ YES /\_\_\_/ | NO /\_\_\_/ Explain: \_\_\_\_\_  
\_\_\_\_\_

Investigation #2  
IND # \_\_\_\_\_ YES /\_\_\_/ | NO /\_\_\_/ 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 /\_\_\_/ Explain: \_\_\_\_\_ | NO /\_\_\_/ Explain: \_\_\_\_\_  
\_\_\_\_\_

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\_\_\_\_\_  
YES /\_\_\_/ Explain \_\_\_\_\_

\_\_\_\_\_  
NO /\_\_\_/ 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 /\_\_\_/

If yes, explain: \_\_\_\_\_  
\_\_\_\_\_

\_\_\_\_\_  
Signature  
Title: CSO

June 1, 1999  
Date

\_\_\_\_\_  
Signature of Division Director

6-1-99  
Date

APPEARS THIS WAY ON ORIGINAL

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



**BCI**<sup>TM</sup>  
*Bone Care International*

One Science Court  
Madison, WI 53711  
Phone: (608) 236-2500  
Fax: (608) 236-2525

As required by Subsection 306 (k)(1) of 21 USC 335 A (k)(1), we hereby certify that in connection with this application, Bone Care International, Inc. did not and will not use in any capacity the services of any person debarred under Section 306 (a) or (b) of the Act.

*Darlene M. Kylo*  
Darlene M. Kylo, RAC

*March 16 1998*  
Date

APPEARS THIS WAY ON ORIGINAL

# Bone Care

INTERNATIONAL

RECEIVED  
5/22

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

ORIGINAL

May 21, 1999

Solomon Sobel, M.D., Director  
Division of Metabolism and Endocrine Drug Products  
Food and Drug Administration  
Center for Drug Evaluation and Research (HFD-510)  
Attn: Document Control Room - 14B19  
5600 Fishers Lane  
Rockville, MD 20857



RE: NDA No. 20-862 for 1-alpha-hydroxyvitamin D<sub>2</sub>: Safety Update

Dear Dr. Sobel:

Enclosed, please find a submission to Bone Care's New Drug Application for 1-alpha-hydroxyvitamin D<sub>2</sub> (doxercalciferol, Hectorol) for the treatment of secondary hyperparathyroidism associated with end-stage renal disease (ESRD).

This submission is being made to update the integrated summary of safety information previously submitted in the NDA, as required by 21 CFR 314.50(d)(5)(vi)(b). The safety update covers the period from November 1, 1997 (the cut-off date for information included in Volume 1 of NDA No. 20-862) through April 18, 1999.

Please contact me at (608) 236-2530 if I can be of any additional assistance.

With best regards,

Darlene M. Kylo, RAC  
Director, Compliance, Quality & Regulatory Affairs

Enclosure

*Handwritten notes:*  
Mylor accepted  
Stress: Hannon had in view of secondary disease  
the studied population, could attribute more points to  
any degree of confidence  
6/1/99

REVIEWS COMPLETED
CSO ACTION:
<input type="checkbox"/> LETTER <input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS _____ DATE _____

**REQUEST FOR TRADEMARK REVIEW**

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

**From:** Division of Metabolic and Endocrine Drug Products/ HFD-510  
Attention: Martin Haber Phone: (301) 827-6388

**Date:** April 30, 1998

**Subject:** Request for Assessment of a Trademark for a Proposed Drug Product

**Proposed Trademark:** Hectorol                      **NDA #:** 20-862

**Company Name:** Bone Care International, Inc.

**Established name, including dosage form:** NA

**Trivial name:** 1- $\alpha$ -hydroxy-Vitamin D<sub>2</sub> capsules

**Dosage form:** 2.5 microgram capsule

**Other trademarks by the same firm for companion products:** NA

**Indications for Use (may be a summary if proposed statement is lengthy):**

Treatment of Hyperparathyroidism in patients with end stage renal disease

**Initial comments from the submitter (concerns, observations, etc.):**

Firm has applied for a USAN name, proposing ercalcidol or ergodiol for consideration. Trivial names also include 1- $\alpha$ -hydroxy-ergocalciferol. The drug substance is a synthetic pro-drug for 1 $\alpha$ ,25-dihydroxy-vitamin D<sub>2</sub>, a naturally occurring active form of vitamin D.

filename: 20862trd.mrk

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

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CDER LABELING AND NOMENCLATURE COMMITTEE

CONSULT # 1017 HFD# 510 PROPOSED PROPRIETARY NAME: PROPOSED ESTABLISHED NAME:  
ATTENTION: MARTIN HABER HECTOROL NA

A. Look-alike/Sound-alike

Potential for confusion:

HEXADROL	Low	XXX	Medium	High
HABITROL	XXX	Low	Medium	High
	Low		Medium	High
	Low		Medium	High
	Low		Medium	High

B. Misleading Aspects:

C. Other Concerns:

--	--

D. Established Name

Satisfactory  
 Unsatisfactory/Reason

Recommended Established Name

E. Proprietary Name Recommendations:

ACCEPTABLE  UNACCEPTABLE  
 WITH CONCERNS

F. Signature of Chair/Date

SI [Redacted]

6/11/98

Meeting Date: October 26, 1998 Time: 9:15 - 10:45 pm Location: 14-56

NDA 20-862 Hectorol (1-alpha-hydroxyvitamin D<sub>2</sub>)

Type of Meeting: General Meeting

External participant: Bone Care International

Meeting Chair: Dr. Gloria Troendle

External participant lead: Ms. Darlene Kylo

Meeting Recorder: Mr. Randy Hedin

FDA Attendees and titles:

Dr. Gloria Troendle, Deputy Division Director DMEDP  
Dr. Leo Lutwak, Medical Reviewer DMEDP  
Dr. Mohammed Al Osh, Reviewer, Division of Biometrics 2  
Mr. Randy Hedin, CSO, DMEDP

External participant Attendees and titles:

Dr. Charles W. Bishop, President  
Ms. Darlene Kylo, Director, Regulatory Affairs

Meeting Objectives:

This meeting was requested by Bone Care International to discuss questions the Division faxed to the firm on October 20, 1998.

Discussion Points:

- The firm provided the attached background document as a response to the Divisions questions.
- A general discussion was held concerning the questions. The firm stated that it will submit a revised document to the NDA in answer to the questions posed by the Division incorporating the explanations and recommendations the Division made.

Decisions (agreements) reached:

- None

Unresolved or issues requiring further discussion:

- None

Action Items:

- The firm will submit revised answers to the questions to the NDA.

Signature, minutes preparer:

/s/ [REDACTED]

Concurrence Chair:

/s/ [REDACTED]

APPEARS THIS WAY ON ORIGINAL

cc: NDA Arch  
HFD-510  
Attendees  
HFD-510/EGalliers  
HFD-511/RHedin/10.26.98/N20862.MN2  
Concurrences: Llutwak/GTroendle/10.26/MAJ Osb/10.27.98

<p><b>RECORD OF TELEPHONE CONVERSATION/MEETING</b></p>	<p><b>Date:</b> June 9, 1999 (3:10 pm)</p>
<p>Re: The sponsor's PI dated 6/9/99</p> <p>I called Ms. Kylo and asked her to make the following changes on the PI which was faxed to me this morning:</p> <ol style="list-style-type: none"> <li><b>1. CLINICAL PHARMACOLOGY:</b> Pharmacokinetics and Metabolism: On the last sentence "Hemodialysis causes a temporary increase in [REDACTED] <math>1\alpha, 25\text{-(OH)}_2\text{D}_2</math> mean concentrations, . . ."</li> <li><b>2. ADVERSE REACTIONS:</b> In the second sentence, "In two placebo-controlled . . . (dosage titrated to achieve target [REDACTED] iPTH levels, see . . .) . . . for two months"</li> <li><b>3. DOSAGE AND ADMINISTRATION:</b> Add "i" before "PTH" in line 7 and 9 of the second paragraph.</li> </ol> <p>I asked her to fax me the revised PI and follow it with a hard copy. She agreed to do so.</p> <p>cc: OrigNDA HFD-510/DivFile HFD-510/Lutwak/Hedin HFD-870/Kavanagh</p> <p>[REDACTED] [REDACTED] [REDACTED]</p> <p>Name: Julie Rhee</p>	<p><b>NDA#: 20-862</b></p> <p><b>Telecon/Meeting initiated by:</b></p> <p>FDA By: Telephone</p> <p><b>Product Name:</b> Hectorol</p> <p><b>Firm Name:</b> Bone Care International</p> <p><b>Name and Title of Person with whom conversation was held:</b> Ms. Darlene Kylo Director, Compliance, Quality, &amp; Regulatory Affairs</p> <p><b>Phone:</b> (608) 236-2530</p>

*Hedin*

NDA 20-862

JAN 28 1999

Bone Care International  
Attention: Ms. Darlene Kylo  
Director, Compliance, Quality, and Regulatory Affairs  
One Science Court  
Madison, WI 53711

Dear Ms. Kylo:

We acknowledge receipt on December 18, 1998, of your December 17, 1998, amendment to your new drug application (NDA) for Hectorol (doxercalciferol) Capsules.

We consider this a major amendment received by the agency within three months of the user fee due date. Therefore, the user fee clock is extended three months. The new due date is June 9, 1999.

If you have any questions, contact Randy Hedin, R.Ph., Senior Regulatory Management Officer, at (301) 827-6392.

Sincerely,



*1/27/99*

Solomon Sobel, M.D.  
Director  
Division of Metabolic and Endocrine Drug  
Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

cc:

Original NDA  
HFD-510/DIVISION FILE  
HFD-510/DIVISION/CSO  
DISTRICT OFFICE



*1/27/99*

APPEARS THIS WAY ON ORIGINAL

Drafted by: RH/January 27, 1999  
Initialed by: EGalliers/1.27/99  
final: RH 1.27.99  
filename: N20862RE.LT1

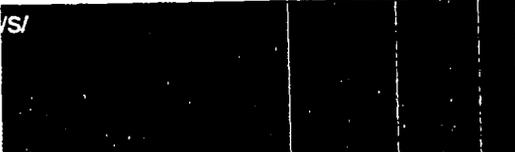
REVIEW EXTENSION

Hedlin

<p><b>RECORD OF TELEPHONE CONVERSATION/MEETING</b></p>	<p><b>DATE:</b> 12/1/98</p>
<p>I called BCI on (11/19) to speak with Darlene M. Kylo, Director of Regulatory Affairs of BCI. When she returned my call I asked for additional information about the safety of several impurities (peaks D and G, &gt;0.1%) which had not been thoroughly qualified in the toxicity testing.</p> <p>Specifically including:</p> <ol style="list-style-type: none"> <li>1) What are the limit specifications for the manufacturing batches?</li> <li>2) What is the worst case maximum amount of each impurity in each capsule?</li> <li>3) What is the maximum daily exposure to patients?</li> <li>4) What is the expected activity/toxicity of these impurities based on their structure and reported activity in the literature or other sources.</li> <li>5) Has BCI studied the effects of these impurities independently?</li> <li>6) Does USP or any other public source of information list these impurities, in similar quantities, as acceptable in any other commercially available preparations.</li> <li>7) Could BCI solicit and submit to the FDA expert opinion about the expected activity and toxicity of the impurities.</li> </ol>	<p><b>NDA NUMBER:</b></p> <p>20-862</p>
<p>Ms Kylo responded that she would fax me the information and also add this information to the official information supplement to the NDA in triplicate.</p> <p>The Fax arrived on 11/30/98 and contains some of the requested information.</p> <p>I called back on 12/1/98 and requested some clarification.</p> <p>Ms Kylo responded that she would add this information to the official information supplement to the NDA in triplicate.</p>	<p><b>PRODUCT NAME:</b></p> <p>Hectorol</p>
<p>[REDACTED]</p>	<p><b>FIRM NAME:</b></p> <p>Bone Care International</p>
<p><b>SIGNATURE:</b> Daniel T. Coleman, Ph.D.</p>	<p><b>DIVISION:</b> DMEDP</p>

CC: HFD-510  
 HFD-510/Coleman, D./Steigerwalt/Hedin.

Hedra

<b>RECORD OF TELEPHONE CONVERSATION/MEETING</b>	<b>DATE: 11/18/98</b>
<p>I called BCI on (11/16) to speak with Darlene M. Kylo, Director of Regulatory Affairs of BCI. When she returned my call I asked for the impurity profiles of the lots of 1aOH-D2 that were used for the following pivotal toxicity studies:</p> <p>1 year monkey study: lot K015, also known as EC1alphaOH9279010</p> <p>1 year rat study: lot K009, also known as EC1alphaOH927904</p> <p>Rabbit segment 2 study: lot K038.</p>	<p><b>NDA NUMBER:</b></p> <p>20-862</p>
<p>How do these impurity profiles compare with the lots used for the clinical trials, and how do they compare with the final marketed product?</p> <p>Ms Kylo responded that she would fax me the information and also submit an official information supplement to the NDA in triplicate.</p> <p>The Fax arrived on 11/18/98 and appears to contain the requested information.</p>	<p><b>PRODUCT NAME:</b></p> <p>Hectorol</p>
<p>APPEARS THIS WAY ON ORIGINAL</p> 	<p><b>FIRM NAME:</b></p> <p>Bone Care International</p>
	
<b>SIGNATURE: Daniel T. Coleman, Ph.D.</b>	<b>DIVISION: DMEDP</b>

CC: HFD-510  
HFD-510/Coleman, D/Steigerwalt/Hedin.

D. Hedlin

<b>RECORD OF TELEPHONE CONVERSATION/MEETING</b>	<b>DATE: 10/29/98</b>
<p>I called BCI on (10/27) to speak with Darlene M. Kylo, Director of Regulatory Affairs of-BCI. When she returned my call I asked:</p> <p>There were excessive deaths in the HD group from the one-year rat study #295-136 performed by [REDACTED]. Histopathology from the next lower dose was inadequate. How long would it take for BCI to submit results of histopathology from all organs on the intermediate dose groups?</p> <p>She said that she would speak with the toxicology coordinator and get back to me.</p>	<p><b>NDA NUMBER:</b></p> <p>20-862</p>
<p>We arranged a conference call for 10/29/98.</p> <p>Participants were:  Daniel T. Coleman, FDA  Darlene M. Kylo, BCI  Joyce Knutson, BCI  Charles Bishop, BCI</p> <p>Darlene referred to the proposed protocol (pages 9-12, pathology section, attached) from IND [REDACTED] for study 295-136 where it states that affected organs will be examined from lower dose groups (page 12). She pointed out that this proposal had been accepted by the FDA (review attached), and suggested that BCI had performed the study as presented in the proposal, and that therefor the study was performed adequately.</p>	<p><b>PRODUCT NAME:</b></p> <p>Hectorol</p>
<p>I read aloud the next paragraph of the proposed protocol (page 12) which states that all tissues from all animals in the next lower dose group would be examined if mortality is high in the HD group. (This paragraph was not included in the final protocol submitted with the study results).</p> <p>Joyce Knutson said that BCI could get the complete histopathology on the 0.55 ug dose group to me by 12/31/98. Charles Bishop agreed that this was possible.</p>	<p><b>FIRM NAME:</b></p> <p>Bone Care International</p>
<p>I asked whether this report could be QAd so fast. They said that they would try.</p> <p>I said I would review the non-QA report pending the QA report and asked that they keep me informed about the timeline.</p> <p>I thanked them for their responsiveness and asked them to try to convert the dosage of Hectorol from micrograms to International Units of Vitamin D activity. [REDACTED]</p>	
<p><b>SIGNATURE: Daniel T. Coleman, Ph.D.</b> [REDACTED] 10/30/98</p>	<p><b>DIVISION: DMEDP</b></p>

CC: HFD-510  
HFD-510/Coleman, D./Hedlin.

10/30/98

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN  
SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND  
RESEARCH  
OFFICE OF CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS  
DIVISION OF PHARMACEUTICAL EVALUATION II

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DATE: June 18, 1998

TO: Darlene Kylo  
Director, Regulatory Affairs  
Bone Care International  
FAX

FROM: Carolyn D. Jones, Ph.D.  
OCPB/DPEII

RE: Sponsor's Request for Suggested Mass Balance Study Design For  
NDA 20-862 (Hectorol®-1-alpha-hydroxyvitamin D<sub>2</sub>)

---

**SYNOPSIS:**

As a follow-up to our telecon of June 2, 1998, I have included the following suggestions to assist you in the design of a mass balance study for Hectorol®.

1. Four healthy subjects would be adequate for this study.
2. As mentioned in the phone conversation, vitamin D is usually labeled with tritium. You would need to include in the study report the following information: radiochemical purity, radioassay, chemical content and specific activity.
3. An intravenous injection can be used.
4. Blood samples should be analyzed at 0, 0.25, 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96, 120, 144 and 168 hours post-dose. An aliquot can be used to quantify total radioactivity and the remainder separated for plasma.
5. Urine should be collected for 7 days following radiolabeled administration. A pre-dose sample should also be collected. On the day of dosing urine can be pooled in the following manner: 0-3, 3-6, 6-12 and 12-24 hours. After this, a pooled daily 24 hour composite sample should be kept.
6. Feces should be collected for 7 days following radiolabeled administration. A pre-dose fecal sample should also be collected. Fecal samples should be pooled daily (24 hour).
7. Duplicate aliquots of the plasma (0.5 ml) and urine (1 ml) samples should be assayed

using a scintillation fluid. Duplicate aliquots should also be analyzed for tritiated water.

8. An acceptable assay for quantitation should be developed.
9. An unlabeled reference standard should be used.
10. The following PK parameters should be evaluated: AUC, C<sub>max</sub>, T<sub>max</sub>, and half-life.
11. The following reference may be helpful—Shimada K et al. Separation and characterization of monoglucuronides of Vitamin D<sub>3</sub> and 25-hydroxyvitamin D<sub>3</sub> in rat bile by high performance liquid chromatography. *Biol Pharm Bull* 1996;4:491-494.

ISI

6/10/98

APPEARS THIS WAY ON ORIGINAL

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DEPARTMENT OF HEALTH & HUMAN SERVICES

*Randy Nevin*  
Public Health Service

Food and Drug Administration  
Rockville MD 20857

NDA 20-862

Bone Care International  
Attention: Darlene M. Kylo, RAC  
One Science Drive  
Madison, WI 53711

MAY 12 1998

Dear Ms. Kylo:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Hectorol (1-alpha-hydroxy-vitamin D<sub>2</sub>) Capsule, 2.5 mcg  
Therapeutic Classification: Standard  
Date of Application: March 7, 1998  
Date of Receipt: March 9, 1998  
Our Reference Number: NDA 20-862

This application was filed under section 505(b) of the Act on May 8, 1998, in accordance with 21 CFR 314.101(a).

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

Sincerely yours,

*5/12/98*

**Enid Galliers**  
Chief, Project Management Staff  
Division of Metabolic and Endocrine Drug Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

NOT POSSIBLE COPY

# Bone Care

INTERNATIONAL

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

June 9, 1999

Solomon Sobel, M.D., Director  
Division of Metabolism and Endocrine Drug Products  
Food and Drug Administration  
Center for Drug Evaluation and Research (HFD-510)  
Attention: Document Control Room - 14B19  
5600 Fishers Lane  
Rockville, MD 20857

RE: NDA No. 20-862 for 1-alpha-hydroxyvitamin D<sub>2</sub> (Hectorol™)

Dear Dr. Sobel:

The following list summarizes the source of intact parathyroid hormone (iPTH) measured in Bone Care's four-controlled clinical trials:

Serum iPTH

Study No. H-106 (Phase 2; open-label)

Plasma iPTH

Study No. H-110 (Phase 2; open-label)

Study No. H-108-LA (Phase 3; double-blind, placebo-controlled)

Study No. H-108-Memphis (Phase 3; double-blind, placebo-controlled)

Please contact me at 608-236-2530 if I can offer additional assistance.

Sincerely,



Darlene M. Kylo, RAC  
Director, Compliance, Quality & Regulatory Affairs

# Bone Care

INTERNATIONAL

One Science Court Madison, WI 53711 Phone: (608) 236-2500 Fax: (608) 236-C314

June 3, 1999

Solomon Sobel, M.D., Director  
Division of Metabolism and Endocrine Drug Products  
Food and Drug Administration  
Center for Drug Evaluation and Research (HFD-510)  
Attention: Document Control Room - 14B19  
5600 Fishers Lane  
Rockville, MD 20857

RE: NDA No. 20-862 for 1-alpha-hydroxyvitamin D<sub>2</sub> (Hectorol™)

Dear Dr. Sobel:

Pursuant to our teleconference with Drs. Leo Lutwak and Gloria Troendle, Randy Hedin, and yourself this morning, and your faxed correspondence dated June 3, 1999, we have prepared and attached a clean copy of the revised label for Hectorol™.

The revised Hectorol™ labeling contains all of the modifications requested by DMEDP today. Specifically, these are:

1. The adverse event table now contains the tabulation of the number of patients who experienced each event, by treatment group, followed by the calculated percentage in parentheses.
2. The "overall" line has been deleted in the adverse event table.
3. The following events have been deleted from the adverse event table:
  - a. Body as a Whole: pain; flu; fever; injured due to fall; pain, chest;
  - b. Cardiovascular System: tachycardia;
  - c. Digestive System: diarrhea; tooth extraction;
  - d. Musculo-Skeletal System: the term "arthrosis" has been *changed to* "arthralgia";
  - e. Nervous System: asthenia;
  - f. Respiratory System: bronchitis; cough; lung disease; pharyngitis; rhinitis;
  - g. Skin: rash.

Solomon Sobel, M.D.

June 3, 1999

Page 2

4. The section under PRECAUTIONS, General, has been replaced with the suggested two paragraphs. References to the drug product have been changed to read "Hectorol" to maintain consistency throughout the labeling.

Sincerely,



Darlene M. Kylo, RAC

Director, Compliance, Quality, & Regulatory Affairs

Enclosure

APPEARS THIS WAY ON ORIGINAL

# Bone Care

INTERNATIONAL

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

June 1, 1999

Solomon Sobel, M.D., Director  
Division of Metabolism and Endocrine Drug Products  
Food and Drug Administration  
Center for Drug Evaluation and Research (HFD-510)  
Attention: Document Control Room - 14B19  
5600 Fishers Lane  
Rockville, MD 20857

RE: NDA No. 20-862 for 1-alpha-hydroxyvitamin D<sub>2</sub> (Hectorol™)

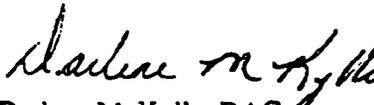
Dear Dr. Sobel:

Pursuant to our teleconference with Dr. Leo Lutwak, Randy Hedin, and yourself this morning, and subsequent conversations with R. Hedin, we have prepared and attached a clean copy of the revised label for Hectorol™.

The revised Hectorol™ labeling contains all of the modifications requested by DMEDP today. Specifically, these are:

1. The adverse event table has been expanded to include the incidence of *all* reportable adverse events (those occurring with a frequency of 2% or greater in the Hectorol™ treatment group) for both active and placebo-treated patients, regardless of causality, during the double-blinded portion of the study;
2. The last sentence under "Carcinogenesis, Mutagenesis, Impairment of Fertility" has been revised as requested by the Pharmacologist; and,
3. A definition has been include for the abbreviation "PTH".

Sincerely,

  
Darlene M. Kylo, RAC  
Director, Compliance, Quality, & Regulatory Affairs

Enclosure

BEST POSSIBLE COPY

# Bone Care

INTERNATIONAL

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

May 27, 1999

Solomon Sobel, M.D., Director  
Division of Metabolism and Endocrine Drug Products  
Food and Drug Administration  
Center for Drug Evaluation and Research (HFD-510)  
Attn: Document Control Room - 14B19  
5600 Fishers Lane  
Rockville, MD 20857

RE: NDA No. 20-862 for 1-alpha-hydroxyvitamin D<sub>2</sub> (Hectorol) Volume 25.1

Dear Dr. Sobel:

Enclosed, please find an information amendment to BCI's New Drug Application for 1-alpha-hydroxyvitamin D<sub>2</sub> (doxercalciferol) for the treatment of secondary hyperparathyroidism associated with end-stage renal disease (ESRD). This information is being submitted as Volume 25.1 to NDA No. 20-862 in response to FDA requests.

Enclosed is:

1. A letter specifying the commitments which Bone Care has agreed to make regarding the above-referenced 4 Phase IV development projects, and
2. A copy of the revised container and carton labels.

Please contact me at (608) 236-2530 if I can be of any additional assistance.

Sincerely,



Darlene M. Kylo, RAC  
Director, Compliance, Quality & Regulatory Affairs

Enclosures

BEST POSSIBLE COPY

# Bone Care

INTERNATIONAL

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

May 27, 1999

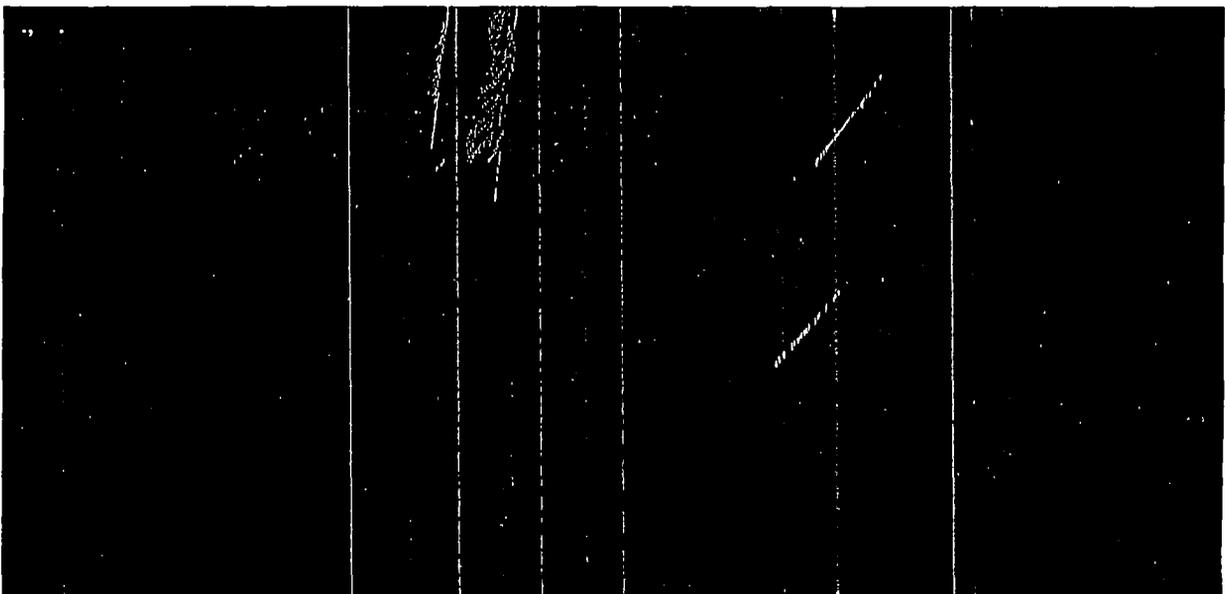
Solomon Sobel, M.D., Director  
Division of Metabolism and Endocrine Drug Products  
Food and Drug Administration  
Center for Drug Evaluation and Research (HFD-510)  
Attn: Document Control Room - 14B19  
5600 Fishers Lane  
Rockville, MD 20857

RE: NDA No. 20-862 for 1-alpha-hydroxyvitamin D2 (Hectorol) Volume 25.1

Dear Dr. Sobel:

Bone Care International commits to the following Phase IV development of [REDACTED]

[REDACTED] On completion of the development, we will submit the [REDACTED]  
and [REDACTED] to the FDA by July 1, 2000, as delineated below.



Sincerely,

*Darlene M. Kylo*

Darlene M. Kylo, RAC  
Director, Compliance, Quality & Regulatory Affairs

# Bone Care

INTERNATIONAL

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

May 21, 1999

Solomon Sobel, M.D., Director  
Division of Metabolism and Endocrine Drug Products  
Food and Drug Administration  
Center for Drug Evaluation and Research (HFD-510)  
Attn: Document Control Room - 14B19  
5600 Fishers Lane  
Rockville, MD 20857

RE: NDA No. 20-862 for 1-alpha-hydroxyvitamin D<sub>2</sub>: Safety Update

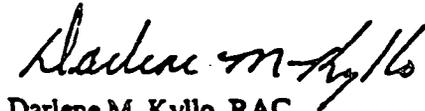
Dear Dr. Sobel:

Enclosed, please find a submission to Bone Care's New Drug Application for 1-alpha-hydroxyvitamin D<sub>2</sub> (doxercalciferol, Hectorol) for the treatment of secondary hyperparathyroidism associated with end-stage renal disease (ESRD).

This submission is being made to update the integrated summary of safety information previously submitted in the NDA, as required by 21 CFR 314.50(d)(5)(vi)(b). The safety update covers the period from November 1, 1997 (the cut-off date for information included in Volume 1 of NDA No. 20-862) through April 18, 1999.

Please contact me at (608) 236-2530 if I can be of any additional assistance.

With best regards,



Darlene M. Kylo, RAC  
Director, Compliance, Quality & Regulatory Affairs

Enclosure

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# Bone Care

INTERNATIONAL

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

May 5, 1999

Gloria J. Troendle, M.D., Deputy Division Director  
Division of Metabolism and Endocrine Drug Products  
Center for Drug Evaluation and Research (HFD-510)  
Food and Drug Administration  
Attn: Document Control Room - 14B19  
5600 Fishers Lane  
Rockville, MD 20857

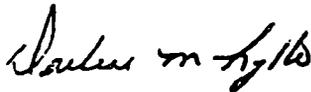
RE: NDA No. 20-862 for Hectorol™ (1-alpha-hydroxyvitamin D<sub>2</sub>, doxercalciferol)

Dear Dr. Troendle:

I am writing to thank you and your colleagues for meeting with representatives from Bone Care International (Bone Care) on Friday, April 9, 1999, to discuss the filing status of our NDA for IV Hectorol, NDA No. 21-027 and to send follow-up correspondence from our Principal Investigators to the above-referenced NDA.

At the meeting, a side discussion arose as to how well dialysis patients as a whole were represented in the patients selected to participate in Bone Care's Phase 3 clinical trials. Drs. Jack Coburn and Russell Chesney, as the Principal Investigators for Bone Care's Phase 3 clinical trials, were instrumental in developing the clinical protocols and selecting the participating patients. They have chosen to write you letters addressing this subject, and they have requested that I send the letters to you.

With best regards,



Darlene M. Kylo, RAC  
Director, Compliance, Quality & Regulatory Affairs

Enclosures

# Bone Care

INTERNATIONAL

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

BC  
NEW DRUG APPLICATION...  
CR100

April 2, 1999

Solomon Sobel, M.D., Director  
Division of Metabolism and Endocrine Drug Products  
Food and Drug Administration  
Center for Drug Evaluation and Research (HFD-510)  
Attn: Document Control Room - 14B19  
5600 Fishers Lane  
Rockville, MD 20857



RE: NDA No. 20-862 for 1-alpha-hydroxyvitamin D<sub>2</sub> (Hectorol); Volume 22.1

Dear Dr. Sobel:

Enclosed, please find an information submission to BCI's New Drug Application for 1-alpha-hydroxyvitamin D<sub>2</sub> (doxercalciferol) for the treatment of secondary hyperparathyroidism associated with end-stage renal disease (ESRD). This information is being submitted as Volume 22.1 to NDA No. 20-862 in response to a request for information.

In a fax dated March 24, 1999, Dr. Duu-Gong Wu relayed comments and information requests which have arisen from the review of the chemistry section. The enclosed submission is the complete response to Dr. Wu's fax.

Please contact me at (608) 236-2530 if I can be of any additional assistance.

Best regards,

*Darlene M. Kylo*  
Darlene M. Kylo, RAC  
Director, Compliance, Quality, & Regulatory Affairs

Enclosure

REVIEWS COMPLETED

CSO ACTION:  
 LETTER  N.A.I.  MEMO

CSO INITIALS \_\_\_\_\_ DATE \_\_\_\_\_

BEST POSSIBLE COPY

# Bone Care

INTERNATIONAL

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

February 12, 1999

Solomon Sobel, M.D., Director  
Division of Metabolism and Endocrine Drug Products  
Food and Drug Administration  
Center for Drug Evaluation and Research (HFD-510)  
Attn: Document Control Room - 14B19  
5600 Fishers Lane  
Rockville, MD 20857

Dear Dr. Sobel:

Enclosed, please find an information amendment to Bone Care International's New Drug Application for 1-alpha-hydroxyvitamin D<sub>2</sub> (1 $\alpha$ -OH-D<sub>2</sub>) for the treatment of secondary hyperparathyroidism associated with end-stage renal disease (ESRD). This information is being submitted as Volume 21.1 to NDA No. 20-862.

In a conference call between DMEDP and Bone Care on January 22, 1999, Dr. Al-Osh requested a repeated measures analysis for the primary endpoint, plasma PTH. Further to this discussion, Dr. Al-Osh clarified his request in a telephone conversation with Dr. Barry Storer, Bone Care's biostatistical consultant and added a request for a non-parametric analysis of the primary endpoint.

Dr. Storer has completed both the repeated measures and non-parametric analyses for the primary endpoint. The data are enclosed.

With best regards,



Darlene M. Kylo, RAC  
Director, Compliance, Quality & Regulatory Affairs

Enclosure

BEST POSSIBLE COPY

# Bone Care

INTERNATIONAL

One Science Court Madison, WI 53711 Phone: (608) 236-2500 Fax: (608) 236-0314  
February 1, 1999

Solomon Sobel, M.D., Director  
Division of Metabolism and Endocrine Drug Products  
Food and Drug Administration  
Center for Drug Evaluation and Research (HFD-510)  
Attn: Document Control Room - 14B19  
5600 Fishers Lane  
Rockville, MD 20857

Dear Dr. Sobel:

Enclosed, please find an information amendment to Bone Care International's New Drug Application for 1-alpha-hydroxyvitamin D<sub>2</sub> (1 $\alpha$ -OH-D<sub>2</sub>) for the treatment of secondary hyperparathyroidism associated with end-stage renal disease (ESRD). This information is being submitted as Volume 20.1 to NDA No. 20-862.

This submission contains Bone Care's responses to a fax from Dr. Gloria Troendle, Deputy Division Director, dated January 21, 1999. The fax contents were discussed and clarified in a conference call involving Dr. Troendle, Dr. Leo Lutwak, Dr. Mohammed Al-Osh, and Mr. Randy Hedin of DMEDP and Dr. Charles Bishop and Ms. Darlene Kylo of BCI.

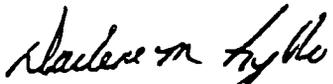
The clinical demographic data requested in the fax are presented in Tables 1 and 2. The demographic data for the 8 subgroups (a through h) are listed for each of two studies: Clinical Study No. H-108-LA in Table 1 and Clinical Study No. H-108-Memphis in Table 2. As further discussed in the telephone conversation on January 22, the requested printouts of the absolute data for PTH, calcium, and phosphorus have been included as Tables 3 through 26, and printed with a landscape orientation. A key to the contents of these tables is listed on the following page.

Finally, the data on the efficacy (plasma PTH) and safety (serum calcium and phosphorus) endpoints have been provided. The data sets are for all patients enrolled in the trials and include each of the identifiers requested by Dr. Al-Osh, following the example provided on page three of the fax. The enclosed diskette contains:

- (1) Eight SAS datasets for Windows (xxx.sd2) - 4 for Los Angeles and 4 for Memphis. Each site has one dataset for demographics, one for PTH, one for calcium, and one for phosphorus,
- (2) A description of the datasets and variables (h108vars.txt), and
- (3) The 3 SAS programs that did the analysis on these datasets (pagexxx.sas).

Hard copy printouts of the above three items accompany the diskette.

With best regards,

  
Darlene M. Kylo, RAC  
Director, Compliance, Quality, & Regulatory Affairs

Enclosure

BEST POSSIBLE COPY

# Bone Care

INTERNATIONAL

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

January 28, 1999



Randy Hedin, R.Ph., RMO  
Division of Metabolism and Endocrine Drug Products  
Food and Drug Administration  
Center for Drug Evaluation and Research (HFD-510)  
Attn: Document Control Room - 14B19  
5600 Fishers Lane  
Rockville, MD 20857

RE: NDA No. 20-862 for 1-alpha-hydroxyvitamin D<sub>2</sub> (Hectorol); Volume 19.1

Dear Randy:

Enclosed is an information submission to BCI's NDA No. 20-862, Volume 19.1, which contains Bone Care's responses to a verbal request from DMEDP's pharmacology reviewer, Dan Coleman.

Dr. Coleman requested that additional histopathological analyses be performed on tissues obtained from a 52-week toxicity study of 1-alpha-hydroxyvitamin D<sub>2</sub> in rats [Study No. 295-136]. This submission contains the audited final report addendum to include a summary of the requested histopathological observations.

To facilitate the report review by the designated reviewers at DMEDP, I have included an additional "desk copy" in this package for the to-be-assigned Pharmacology Reviewer.

Thank you for your continued support. Please contact Darlene M. Kylo, Director of Compliance, Quality, and Regulatory Affairs, at (608) 236-2530 if any additional assistance is needed.

With best regards,

A handwritten signature in cursive script that reads "Charles W. Bishop".

Charles W. Bishop, Ph.D.  
President

Enclosure

BEST POSSIBLE COPY

# Bone Care

INTERNATIONAL

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

January 28, 1999

Solomon Sobel, M.D., Director  
Division of Metabolism and Endocrine Drug Products  
Food and Drug Administration  
Center for Drug Evaluation and Research (HFD-510)  
Attn: Document Control Room - 14B19  
5600 Fishers Lane  
Rockville, MD 20857

RE: NDA No. 20-862 for 1-alpha-hydroxyvitamin D<sub>2</sub> (Hectorol); Volume 19.1

Dear Dr. Sobel:

Enclosed is an information submission to BCI's NDA No. 20-862, Volume 19.1, which contains Bone Care's responses to a verbal request from DMEDP's pharmacology reviewer, Dan Coleman.

Dr. Coleman requested that additional histopathological analyses be performed on tissues obtained from a 52-week toxicity study of 1-alpha-hydroxyvitamin D<sub>2</sub> in rats [Study No. ■■■■■ 295-136]. This submission contains the audited final report addendum to include a summary of the histopathological observations.

Please contact Darlene M. Kylo, Director of Compliance, Quality and Regulatory Affairs at (608) 236-2530 if any additional assistance is needed.

With best regards,



Charles W. Bishop, Ph.D.  
President

# Bone Care

INTERNATIONAL

ORIGINAL

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

ORIG AMENDMENT

BS

January 14, 1999



Solomon Sobel, M.D., Director  
Division of Metabolism and Endocrine Drug Products  
Food and Drug Administration  
Center for Drug Evaluation and Research (HFD-510)  
Attention: Document Control Room - 14B19  
5600 Fishers Lane  
Rockville, MD 20857

RE: NDA No. 20-862 for 1-alpha-hydroxyvitamin D<sub>2</sub> (Hectorol); Volume 18.1

Dear Dr. Sobel:

Enclosed, please find an electronic copy of the statistical re-analysis performed in SAS on the pivotal Phase 3 clinical studies. The re-analysis of the data was requested by DMEDP on October 20 and 26, 1998, and portions of the re-analysis were submitted by BCI to this NDA as they were completed on December 3, 7, 14, and 17, 1998.

The data in these 4 submissions were originally sent both as hard copies and electronically in WordPerfect. The 3 1/2" diskettes (2) enclosed, containing the datasets and SAS programs used to re-analyze the clinical data, were requested by Randy Hedin, R.Ph., RMO, today, January 14, 1999.

Mr. Hedin also requested a replacement diskette for SAS datasets and programs used in the original analysis of data from Clinical Study No. H-108-LA. The diskette containing the information in SAS, originally submitted in Volume 3.1 on April 27, 1998, was defective and the data was corrupted.

Best regards,

*Darlene M. Kylo*  
Darlene M. Kylo, RAC  
Director, Regulatory Affairs

Enclosures

*To Bureau*  
SI  
*Dr. Hedin has data copy 1/14/99*  
SI

REVIEWS COMPLETED	
CSO ACTION:	
<input type="checkbox"/> LETTER	<input type="checkbox"/> N.A.L. <input type="checkbox"/> MEMO
CSO INITIALS	DATE

# Bone Care

INTERNATIONAL

One Science Court Madison, WI 53711 Phone: (608) 236-2500 Fax: (608) 236-2314

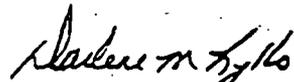
January 14, 1999

Solomon Sobel, M.D., Director  
Division of Metabolism and Endocrine Drug Products  
Food and Drug Administration  
Center for Drug Evaluation and Research (HFD-510)  
Attention: Document Control Room - 14B19  
5600 Fishers Lane  
Rockville, MD 20857

Dear Dr. Sobel:

Bone Care International recognizes that Volume 13, submitted to NDA No. 20-862 on December 17, 1998, constitutes a major amendment as defined by 21 CFR 314.60. As this amendment was submitted within 90 days of the PDUFA review date, March 9, 1999, Bone Care agrees with DMEDP that the User Fee review date will be extended by 90 days. The new User Fee review date will be June 9, 1999.

Best regards,

  
Darlene M. Kylló, RAC  
Director, Regulatory Affairs

APPEARS THIS WAY ON ORIGINAL

# Bone Care

INTERNATIONAL

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

January 12, 1999

Solomon Sobel, M.D., Director  
Division of Metabolism and Endocrine Drug Products  
Food and Drug Administration  
Center for Drug Evaluation and Research (HFD-510)  
Attn: Document Control Room - 14B19  
5600 Fishers Lane  
Rockville, MD 20857

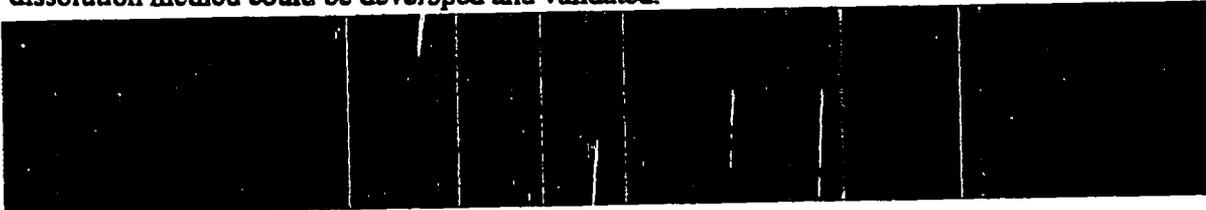


RE: NDA No. 20-862 for 1-alpha-hydroxyvitamin D<sub>2</sub> (Hectorol); Volume 17.1

Dear Dr. Sobel:

Enclosed is an information submission to BCI's NDA No. 20-862 which contains Bone Care's responses to a fax from Dr. Hae-Young Ahn, DMEDP Biopharmaceutics Reviewer. The enclosed report, Volume 17.1, summarizes Bone Care's research and development of a working dissolution method for Hectorol capsules.

In her fax, dated May 12, 1998, Dr. Ahn requested that dissolution studies be conducted on the Hectorol soft gelatin capsules and that the data be submitted for review. Bone Care agreed with DMEDP's request (written confirmation sent July 16, 1998, as Volume 4.1) fully believing that a dissolution method could be developed and validated.



We respectfully request you review the development work summary enclosed and consider granting Bone Care the option to test Hectorol capsules using the disintegration method.

Thank you in advance for your continued support. Please contact me at (608) 236-2530 if I can be of any additional assistance.

With best regards,

A handwritten signature in cursive script, appearing to read "Darlene M. Kylo".

Darlene M. Kylo, RAC  
Director, Regulatory Affairs

Enclosure

# Bone Care

INTERNATIONAL

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

December 30, 1998

Solomon Sobel, M.D., Director  
Division of Metabolism and Endocrine Drug Products  
Food and Drug Administration  
Center for Drug Evaluation and Research (HFD-510)  
Attn: Document Control Room - 14B19  
5600 Fishers Lane  
Rockville, MD 20857

RE: NDA No. 20-862 for 1-alpha-hydroxyvitamin D<sub>2</sub> (Hectorol); Volume 16.1

Dear Dr. Sobel:

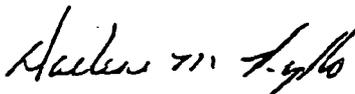
Enclosed, please find an information amendment to Bone Care International's New Drug Application for 1-alpha-hydroxyvitamin D<sub>2</sub> (1 $\alpha$ -OH-D<sub>2</sub>) for the treatment of secondary hyperparathyroidism associated with end-stage renal disease (ESRD). This information, being submitted as Volume 16.1 to NDA No. 20-862, contains a (draft) supplemental histopathology report for Bone Care's preclinical study, Study No. IRDC 295-136.

Dan Coleman, Ph.D., Pharmacology Reviewer, requested on October 29, 1998, that additional analysis be performed on tissue which was obtained from animals dosed in the 52-week, rat, chronic toxicity study, Study No. [REDACTED] 295-136. Dr. Coleman further requested a draft report by the end of December to complete his review by January 1999. Bone Care agreed to have the analysis done, to submit a draft, unaudited report by the end of December, and to follow the draft report with a final report.

To facilitate the report review by the designated reviewers at DMEDP, I have included an additional "desk copy" in this package for the to-be-assigned Pharmacology Reviewer.

Please contact me at (608) 236-2530 if I can be of any additional assistance.

With best regards,

  
Darlene M. Kylo, RAC  
Director, Compliance, Quality & Regulatory Affairs

DMK/klb

Enclosure

# Bone Care

INTERNATIONAL

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

December 23, 1998

Solomon Sobel, M.D., Director  
Division of Metabolism and Endocrine Drug Products  
Food and Drug Administration  
Center for Drug Evaluation and Research (HFD-510)  
Attn: Document Control Room - 14B19  
5600 Fishers Lane  
Rockville, MD 20857



RE: NDA No. 20-862 for 1-alpha-hydroxyvitamin D<sub>2</sub> (Hectorol); Volume 15.1

Dear Dr. Sobel:

Enclosed, please find an information amendment to Bone Care International's New Drug Application for 1-alpha-hydroxyvitamin D<sub>2</sub> (1 $\alpha$ -OH-D<sub>2</sub>) for the treatment of secondary hyperparathyroidism associated with end-stage renal disease (ESRD). This information is being submitted as Volume 15.1 to NDA No. 20-862.

This submission contains Bone Care's responses to a verbal request from DMEDP's pharmacology reviewer, Dan Coleman.



This submission contains the data requested. Please contact me at (608) 236-2530 if I can be of any additional assistance.

With best regards,

A handwritten signature in cursive script that reads "Darlene M. Kylo".

Darlene M. Kylo, RAC  
Director, Regulatory Affairs

DMK/klb

BEST POSSIBLE COPY

# Bone Care

INTERNATIONAL

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

December 22, 1998

Solomon Sobel, M.D., Director  
Division of Metabolism and Endocrine Drug Products  
Food and Drug Administration  
Center for Drug Evaluation and Research (HFD-510)  
Attn: Document Control Room - 14B19  
5600 Fishers Lane  
Rockville, MD 20857



RE: NDA No. 20-862 for 1-alpha-hydroxyvitamin D<sub>2</sub> (Hectorol); Volume 14.1

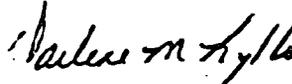
Dear Dr. Sobel:

Enclosed, please find an information amendment to BCI's New Drug Application for 1-alpha-hydroxyvitamin D<sub>2</sub> (1 $\alpha$ -OH-D<sub>2</sub>) for the treatment of secondary hyperparathyroidism associated with end-stage renal disease (ESRD). This information is being submitted as Volume 14.1 to NDA No. 20-862.

The previous submissions to this NDA for serum osteocalcin and bone specific alkaline phosphatase contained data from samples obtained at baseline, week 4, week 16, and week 24. Volume 14.1, enclosed, incorporates additional osteocalcin and bone alkaline phosphatase data from recently analyzed 8- and 12-week time points. The data is expressed as both absolute and relative values.

Please contact me at (608) 236-2530 if I can be of any additional assistance.

With best regards,

  
Darlene M. Kylo, RAC  
Director, Regulatory Affairs

DMK/klb

Enclosure

BEST POSSIBLE COPY

# Bone Care

INTERNATIONAL

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

December 17, 1998

Solomon Sobel, M.D., Director  
Division of Metabolism and Endocrine Drug Products  
Food and Drug Administration  
Center for Drug Evaluation and Research (HFD-510)  
Attn: Document Control Room - 14B19  
5600 Fishers Lane  
Rockville, MD 20857



RE: NDA No. 20-862 for 1-alpha-hydroxyvitamin D<sub>2</sub> (Hectorol); Volume

Dear Dr. Sobel:

Enclosed, please find an information submission to BCI's New Drug Application for 1-alpha-hydroxyvitamin D<sub>2</sub> (1 $\alpha$ -OH-D<sub>2</sub>) for the treatment of secondary hyperparathyroidism associated with end-stage renal disease (ESRD). This information is being submitted as Volume 13 to NDA No. 20-862 in response to a request for information.

In a fax dated October 20, 1998, Randy Hedin relayed comments and information requests from the Medical and Statistical Reviewers. BCI formulated an initial response to the requests and discussed each request and proposed response at a meeting with DMEDP staff on Monday, October 26, 1998.

Four information submissions addressing the discussed comments and requests have been submitted to date: Volume 9.1 on November 24, 1998; Volume 10.1 on December 3, 1998; Volume 11.1 on December 7, 1998; and Volumes 12.1, 12.2, and 12.3 on December 14, 1998.

Volumes 13.1, and 13.2, enclosed, contain: (1) the statistical re-analysis of the percent change from baseline for the remaining chemistry parameters, and the hematology, and serum bone markers, and (2) the corresponding plots of responses, linear vs. time, for the serum bone markers (osteocalcin and bone specific alkaline phosphatase).

Please contact me at (608) 236-2530 if I can be of any additional assistance.

With best regards,

*Darlene M. Kylo (bcb)*

Darlene M. Kylo, RAC  
Director, Regulatory Affairs

Enclosure

# Bone Care

INTERNATIONAL

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

December 14, 1998

Solomon Sobel, M.D., Director  
Division of Metabolism and Endocrine Drug Products  
Food and Drug Administration  
Center for Drug Evaluation and Research (HFD-510)  
Attn: Document Control Room - 14B19  
5600 Fishers Lane  
Rockville, MD 20857



RE: NDA No. 20-862 for 1-alpha-hydroxyvitamin D<sub>2</sub> (Hectorol); Volume 12

Dear Dr. Sobel:

Enclosed, please find an information submission to BCI's New Drug Application for 1-alpha-hydroxyvitamin D<sub>2</sub> (1 $\alpha$ -OH-D<sub>2</sub>) for the treatment of secondary hyperparathyroidism associated with end-stage renal disease (ESRD). This information is being submitted as Volume 12 to NDA No. 20-862 in response to a request for information.

In a fax dated October 20, 1998, Randy Hedin relayed comments and information requests from the Medical and Statistical Reviewers. BCI formulated an initial response to the requests and discussed each request and proposed response at a meeting with DMEDP staff on Monday, October 26, 1998.

Three information submissions addressing the discussed comments and requests have been submitted to date: Volume 9.1 on November 24, 1998, Volume 10.1 on December 3, 1998, and Volume 11.1 on December 7, 1998.

Volumes 12.1, 12.2, and 12.3, enclosed, contain: (1) the statistical re-analysis of the absolute data for the remaining chemistry parameters, and the hematology, vitamin D, and serum bone markers, and (2) the corresponding plots of responses, linear vs. time, for the serum bone markers (osteocalcin and bone specific alkaline phosphatase).

Please contact me at (608) 236-2530 if I can be of any additional assistance.

With best regards,

A handwritten signature in cursive script that reads "Darlene M. Kylo". The signature is written in dark ink and is positioned above the typed name.

Darlene M. Kylo, RAC  
Director, Regulatory Affairs

Enclosure

# Bone Care

INTERNATIONAL

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

December 7, 1998

Solomon Sobel, M.D., Director  
Division of Metabolism and Endocrine Drug Products  
Food and Drug Administration  
Center for Drug Evaluation and Research (HFD-510)  
Attn: Document Control Room - 14B19  
5600 Fishers Lane  
Rockville, MD 20857



RE: NDA No. 20-862 for 1-alpha-hydroxyvitamin D<sub>2</sub> (Hectorol); Volume 11.1

Dear Dr. Sobel:

Enclosed, please find an information submission to BCI's New Drug Application for 1-alpha-hydroxyvitamin D<sub>2</sub> (1 $\alpha$ -OH-D<sub>2</sub>) for the treatment of secondary hyperparathyroidism associated with end-stage renal disease (ESRD). This information is being submitted as Volume 11.1 to NDA No. 20-862 in response to a request for information.

In a fax dated October 20, 1998, Ruddy Hedin relayed comments and information requests from the Medical and Statistical Reviewers. BCI formulated an initial response to the requests and discussed each request and proposed response at a meeting with DMEDP staff on Monday, October 26, 1998.

Two information submissions addressing the discussed comments and requests have been submitted to date: Volume 9.1 on November 24, 1998, and Volume 10.1 on December 3, 1998.

Volume 11.1, enclosed, contains: (1) the statistical re-analysis, as a percent of baseline, of the two key clinical safety parameters, serum calcium and phosphorus, and the key efficacy parameter, PTH, and (2) the corresponding plots of responses, linear vs. time, for the PTH, calcium, and phosphorus data as a percent of baseline.

Please contact me at (608) 236-2530 if I can be of any additional assistance.

With best regards,

A handwritten signature in cursive script that reads "Darlene M. Kylo".

Darlene M. Kylo, RAC  
Director, Regulatory Affairs

Enclosure

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# Bone Care

INTERNATIONAL

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

December 3, 1998

Solomon Sobel, M.D., Director  
Division of Metabolism and Endocrine Drug Products  
Food and Drug Administration  
Center for Drug Evaluation and Research (HFD-510)  
Attn: Document Control Room - 14B19  
5600 Fishers Lane  
Rockville, MD 20857



RE: NDA No. 20-862 for 1-alpha-hydroxyvitamin D<sub>2</sub> (Hectorol); Volume 10.1

Dear Dr. Sobel:

Enclosed, please find an information submission to BCI's New Drug Application for 1-alpha-hydroxyvitamin D<sub>2</sub> (1 $\alpha$ -OH-D<sub>2</sub>) for the treatment of secondary hyperparathyroidism associated with end-stage renal disease (ESRD). This information is being submitted as Volume 10.1 to NDA No. 20-862 in response to a request for information.

In a fax dated October 20, 1998, Randy Hedin relayed comments and information requests from the Medical and Statistical Reviewers. BCI formulated an initial response to the requests and discussed each request and proposed response at a meeting with DMEDP staff on Monday, October 26, 1998.

An information submission addressing the discussed comments and requests was submitted to this NDA on November 24, 1998, in Volume 9.1. It was incomplete in that it contained (1) the requested summary demographic information from only 5 of the 18 Phase 3 clinical sites and (2) the statistical re-analysis for only the key efficacy parameter, plasma intact PTH.

Volume 10.1, enclosed, contains: (1) the summary demographic data from all 18 clinical sites; (2) the statistical re-analysis of the two clinical study safety parameters, serum calcium and phosphorus, along with a resubmission of the *corrected* PTH data; and (3) the corresponding plots of responses, linear vs. time, for the PTH, calcium, and phosphorus data.

Errors were discovered in the PTH statistical analyses following the submission of Volume 9.1 to the FDA. Those errors have now been corrected and the tables in Volume 9.1 are fully replaced with new summaries in Volume 10.1. The software program used to "fill-in" the missing laboratory data and generate the statistics is being retested prior to providing the remaining ancillary data (hematology and chemistry profile reanalyses) still outstanding.

BEST POSSIBLE COPY

Solomon Sobel, M.D.  
December 3, 1998  
Page 2

We sincerely apologize for the time required to respond to this request for information. We feel very strongly that the data provided to DMEDP be fully accurate and we ask for your continued patience.

Please contact me at (608) 236-2530 if I can be of any additional assistance.

With best regards,

*Darlene M. Kylo*  
Darlene M. Kylo, RAC  
Director, Regulatory Affairs

Enclosure

BEST POSSIBLE COPY

# Bone Care

INTERNATIONAL

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

November 24, 1998

Solomon Sobel, M.D., Director  
Division of Metabolism and Endocrine Drug Products  
Food and Drug Administration  
Center for Drug Evaluation and Research (HFD-510)  
Attn: Document Control Room - 14B19  
5600 Fishers Lane  
Rockville, MD 20857



RE: NDA No. 20-862 for 1-alpha-hydroxyvitamin D<sub>2</sub> (Hectorol); Volume 9.1

Dear Dr. Sobel:

Enclosed, please find an information submission to BCI's New Drug Application for 1-alpha-hydroxyvitamin D<sub>2</sub> (1 $\alpha$ -OH-D<sub>2</sub>) for the treatment of secondary hyperparathyroidism associated with end-stage renal disease (ESRD). This information is being submitted as Volume 9.1 to NDA No. 20-862 in response to a request for information.

In a fax dated October 20, 1998, Randy Hedin relayed comments and information requests from the Medical and Statistical Reviewers. BCI formulated an initial response to the requests and discussed each request and proposed response at a meeting with DMEDP staff on Monday, October 26, 1998. Present at the meeting were Gloria Troendle, M.D., Leo Lutwak, M.D., Mohammed Al-Osh, Ph.D., and Randy Hedin, R.Ph. (from DMEDP), and Charles Bishop, Ph.D. and Darlene Killo (from BCI).

The enclosed submission is the initial information submission to this NDA in response to the October 20, 1998, fax. It has been modified to incorporate what was discussed and agreed upon at the meeting at DMEDP's offices with 2 exceptions:

1. The patient demographic information has been received from only 5 of the 18 dialysis sites. This data is included and will be updated when the remainder is received.
2. BCI is still processing the requested statistical analyses and plans to submit all analyses no later than the week of December 7, 1998. The data being re-processed are from Clinical Study H-108-LA and H-108-Memphis. The end product of the re-analysis will be summary tables which include (1) data from untreated patients who participated in the washout period only and (2) missing lab

Solomon Sobel, M.D.  
November 24, 1998  
Page 2

data filled in with the most recent value previously obtained. For each of the 32 parameters measured, the following 18 tables will be provided:

- a. Non-treated patients randomized to active or placebo treatment (n = 73);
- b. All patients randomized to active or placebo treatment (n = 211);
- c. Non-treated patients randomized to active treatment (n = 34);
- d. All patients randomized to active treatment (n = 104);
- e. Non-treated patients randomized to placebo treatment (n = 39);
- f. All patients randomized to placebo treatment (n = 106);
- g. Non-treated LA patients randomized to active or placebo treatment (n = 42);
- h. All LA patients randomized to active or placebo treatment (n = 104);
- i. Non-treated LA patients randomized to active treatment (n = 22);
- j. All LA patients randomized to active treatment (n = 52);
- k. Non-treated LA patients randomized to placebo treatment (n = 20);
- l. All LA patients randomized to placebo treatment (n = 52);
- m. Non-treated Memphis patients randomized to active or placebo treatment (n = 31);
- n. All Memphis patients randomized to active or placebo treatment (n = 107);
- o. Non-treated Memphis patients randomized to active treatment (n = 12);
- p. All Memphis patients randomized to active treatment (n = 53);
- q. Non-treated Memphis patients randomized to placebo treatment (n = 19);  
and,
- r. All Memphis patients randomized to placebo treatment (n = 54).

Further, 9 of the 18 above tables will be submitted for the percent change from baseline analysis (tables b, d, f, h, j, l, n, p, and r).

Enclosed is both a hard copy and electronic format (diskette) for this submission. The diskette contains the text response and the tables in Appendix II in WordPerfect 7.0 format.

Please contact me at (608) 236-2530 if I can be of any additional assistance.

Best regards,

  
Darlene M. Kylo, RAC  
Director, Regulatory Affairs

Enclosure

BEST POSSIBLE COPY

# Bone Care

INTERNATIONAL

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

November 16, 1998

Solomon Sobel, M.D., Director  
Division of Metabolism and Endocrine Drug Products  
Food and Drug Administration  
Center for Drug Evaluation and Research (HFD-510)  
Attn: Document Control Room - 14B19  
5600 Fishers Lane  
Rockville, MD 20857

RE: NDA No. 20-862 for 1-alpha-hydroxyvitamin D<sub>2</sub> (Hectorol); Volume 8.1

Dear Dr. Sobel:

Enclosed, please find an information submission to BCI's New Drug Application for 1-alpha-hydroxyvitamin D<sub>2</sub> (1 $\alpha$ -OH-D<sub>2</sub>) for the treatment of secondary hyperparathyroidism associated with end-stage renal disease (ESRD). This information is being submitted as Volume 8.1 to NDA No. 20-862 in response to a request for information.

In a fax dated May 12, 1998, Dr. Hae-Young Ahn, biopharmaceutician, requested submission of a study to support the metabolism and protein binding data for humans presented in the summary section. The enclosed submission is the final report and analysis for the protein binding study conducted in response to Dr. Ahn's request.

Enclosed is both a hard copy and electronic format (diskette) for this submission. The diskette contains the report, tables, and figures in MS Word format, the appendices are in Excel 97.

Please contact me at (608) 236-2530 if I can be of any additional assistance.

Best regards,

  
Darlene M. Kylo, RAC  
Director, Regulatory Affairs

Enclosure

# Bone Care

INTERNATIONAL

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

November 5, 1998

Solomon Sobel, M.D., Director  
Division of Metabolism and Endocrine Drug Products  
Food and Drug Administration  
Center for Drug Evaluation and Research (HFD-510)  
Attn: Document Control Room - 14B19  
5600 Fishers Lane  
Rockville, MD 20857

RE: NDA No. 20-862 for 1-alpha-hydroxyvitamin D<sub>2</sub> (Hectorol); Volume 7.1

Dear Dr. Sobel:

Enclosed, please find an information submission to BCI's New Drug Application for 1-alpha-hydroxyvitamin D<sub>2</sub> (1 $\alpha$ -OH-D<sub>2</sub>) for the treatment of secondary hyperparathyroidism associated with end-stage renal disease (ESRD). This pharmacokinetic information is being submitted as Volume 7.1 to NDA No. 20-862 in response to a request for information.

In a fax dated May 12, 1998, Dr. Hae-Young Ahn, biopharmaceutician, recommended that a pharmacokinetic study be conducted in patients with hepatic impairment. The enclosed submission is the final report and analysis for the pharmacokinetic study in 12 hepatically impaired patients and 4 normal, healthy subjects.

Dr. Ahn also requested that a pharmacokinetic study in the target population (ESRD patients) and a protein binding study be performed. We have completed both of these studies; the final report for the ESRD pharmacokinetic study was submitted to this NDA yesterday and the protein binding study report will be submitted shortly.

Please contact me at (608) 236-2530 if I can be of any additional assistance.

Best regards,



Darlene M. Kylo, RAC  
Director, Regulatory Affairs

Enclosure

# Bone Care

INTERNATIONAL

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

November 4, 1998

Solomon Sobel, M.D., Director  
Division of Metabolism and Endocrine Drug Products  
Food and Drug Administration  
Center for Drug Evaluation and Research (HFD-510)  
Attn: Document Control Room - 14B19  
5600 Fishers Lane  
Rockville, MD 20857



RE: NDA No. 20-862 for 1-alpha-hydroxyvitamin D<sub>2</sub> (Hectorol); Volume 6.1

Dear Dr. Sobel:

Enclosed, please find an information submission to BCI's New Drug Application for 1-alpha-hydroxyvitamin D<sub>2</sub> (1 $\alpha$ -OH-D<sub>2</sub>) for the treatment of secondary hyperparathyroidism associated with end-stage renal disease (ESRD). This pharmacokinetic information is being submitted as Volume 6.1 to NDA No. 20-862 in response to a request for information.

In a fax dated May 12, 1998, Dr. Hae-Young Ahn, biopharmaceutician, requested that a pharmacokinetic study in the target population, ESRD patients, be conducted. The enclosed submission is the final report and analysis for the pharmacokinetic study in ESRD patients.

Dr. Ahn also recommended that an hepatic impairment pharmacokinetic study and a protein binding study be performed. We have completed both of these studies and will submit the final report for the hepatic pharmacokinetic study to this NDA within the next two days and the protein binding study report shortly thereafter.

Please contact me at (608) 236-2530 if I can be of any additional assistance.

Best regards,

A handwritten signature in cursive script that reads "Darlene M. Kylo".

Darlene M. Kylo, RAC  
Director, Regulatory Affairs

**BCI™**

*Bone Care International*

One Science Court  
Madison, WI 53711  
Phone: (608) 236-2500  
Fax: (608) 236-2525

April 27, 1998

Solomon Sobel, M.D., Director  
Division of Metabolism and Endocrine Drug Products  
Food and Drug Administration  
Center for Drug Evaluation and Research (HFD-510)  
Attention: Document Control Room - 14B19  
5600 Fishers Lane  
Rockville, MD 20857

Dear Dr. Sobel:

Enclosed, please find additional information to BCI's New Drug Application for 1-alpha-hydroxyvitamin D<sub>2</sub> (1 $\alpha$ -OH-D<sub>2</sub>) for the treatment of secondary hyperparathyroidism associated with end-stage renal disease (ESRD). This information is being submitted as Volume 3.1 to NDA No. 20-862.

An electronic copy of the statistical analyses performed in SAS on the pivotal Phase 3 clinical studies and the supporting Phase 2 clinical studies is enclosed in response to DMEDP's request for information. The telephone request was made by Randy Hedin, R.Ph., CSO, on Monday, April 20, 1998.

Specifically, the 3 1/2" diskettes contain the datasets and SAS programs used to analyze the efficacy parameters and the baseline comparative demographic data from BCI's pivotal Phase 3 and supporting Phase 2 clinical trials.

A hard copy which lists the dataset files and printouts of the SAS programs used for the analyses preface the diskettes. This is organized by clinical study protocol number.

Please contact me at (608) 236-2530 if I can be of additional assistance.

Best regards,



Darlene M. Kylo, RAC  
Director, Regulatory Affairs

Enclosure

**BCI**<sup>TM</sup>

*Bone Care International*

One Science Court  
Madison, WI 53711  
Phone: (608) 236-2500  
Fax: (608) 236-2525

March 25, 1998

Dr. Leo Letwak  
Division of Metabolism and Endocrine Drug Products  
Food and Drug Administration  
Center for Drug Evaluation and Research (HFD-510)  
Attn: Document Control Room - 14B19  
5600 Fishers Lane  
Rockville, MD 20857

RE: Bone Care International, Inc.  
NDA No. 20-862

Dear Dr. Letwak:

Per your request, enclosed please find an electronic copy, in PDF format, of the above-mentioned NDA. This NDA was received by the FDA in hard copy on March 9, 1998.

Attached you will find a listing of the actual PDF files which indicates how each volume of the NDA has been named on the disks. For example, Volume 1.1 is named "BCARE101.PDF" on the disk, and Volume 1.45 is named "BCARE145.PDF." The attachment also explains at the bottom that a few files were too large to fit on one disk and therefore were split between two disks.

We are loaning the enclosed zip drive to you for your use in reading these disks. Please note that you will need to install the user disk before reading the files.

I hope that you find this electronic format helpful in your review. Please let me know if you require anything further.

Best regards,



Charles W. Bishop, Ph.D.  
President

Enclosure

**BCI**<sup>TM</sup>  
Bone Care International

COPY

One Science Court  
Madison, WI 53711  
Phone: (608) 236-2500  
Fax: (608) 236-2525

March 16, 1998

From: Vol. 2.1  
NDA # 20-862

Solomon Sobel, M.D., Director  
Division of Metabolism and Endocrine Drug Products  
Food and Drug Administration  
Center for Drug Evaluation and Research (HFD-510)  
Attention: Document Control Room - 14B19  
5600 Fishers Lane  
Rockville, MD 20857

Dear Dr. Sobel:

Enclosed, please find additional information to Bone Care International's (BCI) new drug application for 1-alpha-hydroxyvitamin D<sub>2</sub> (1 $\alpha$ -OH-D<sub>2</sub>) for the treatment of secondary hyperparathyroidism associated with end-stage renal disease (ESRD), NDA No. 20-862.

These 3 items are being submitted in response to the Division of Metabolism and Endocrine Drug Products' (DMEDP) request for information per my telephone conversation with Randy Hedin, R.Ph., CSO, on Wednesday, March 11, 1998.

1. A request for a United States Adopted Name (USAN) has been submitted to the USAN Council. A copy of the USANC Submission Form 1002 is enclosed.
2. A Statement of Debarment Certification.
3. Certification that the Field Copy has been submitted to the District Office.

I trust this satisfies DMEDP's request for information at this time. Please contact me at (608) 236-2530 if I can be of additional assistance.

Best regards,

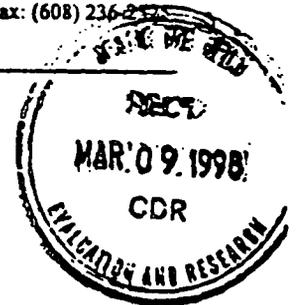
  
Darlene M. Kylo, RAC  
Director, Regulatory Affairs

Enclosure

**BCI**<sup>TM</sup>  
Bone Care International



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



March 7, 1998

Solomon Sobel, M.D., Director  
Division of Metabolism and Endocrine Drug Products  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Central Documents Room  
12229 Wilkes Avenue  
Rockville, MD 20852

MAR

Dear Dr. Sobel:

Bone Care International is pleased to submit with this letter our New Drug Application for 1-alpha-hydroxyvitamin D<sub>2</sub> (1α-OH-D<sub>2</sub>, Hectorol), NDA No. 20-862.

BCI has been developing 1α-OH-D<sub>2</sub> as a treatment for secondary hyperparathyroidism in end stage renal disease (ESRD) patients under IND File No. [redacted]. The proposed drug product is formulated as a [redacted]. The recommended dosage is oral administration three times per week following hemodialysis. We believe that 1α-OH-D<sub>2</sub> offers a significant improvement in treatment over the currently available therapy with significant efficacy responses of 96.7 to 100.0% in treated patients participating in well-controlled trials.

BCI respectfully requests a priority review status for 1α-OH-D<sub>2</sub>.

Please also find enclosed a letter from Suzanne M. O'Shea, Department of Health & Human Services, Food and Drug Administration, dated February 3, 1998, granting a small business waiver to BCI for the application fee payment [redacted].

To aid the reviewers' determination of the application completeness, please note that the statements of compliance with 21CFR Part 58 for nonclinical laboratory studies are located in Volume 1.5, Page 007; the statements of compliance with 21 CFR Parts 50 and 56 for clinical studies conducted in the U.S. are located in Volume 1.42, Pages 128 - 138; and the statement of compliance for clinical studies conducted outside the U.S. ([redacted]) is located in Volume 1.1, Page 049.

Thank you for your ongoing support of BCI's development program for 1α-OH-D<sub>2</sub>.

Best regards,

*Darlene M. Kylo*  
Darlene M. Kylo, RAC  
Director, Regulatory Affairs

Enclosure