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

March 13, 2000

John K. Jenkins, M.D., Acting Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Food and Drug Administration
Center for Drug Evaluation and Research (HFD-510)
Attention: Document Control Room
5600 Fishers Lane
Rockville, MD 20857

RE: NDA No. 21-027 for Hectorol (doxercalciferol) Injection, Volume 11.1

Dear Dr. Jenkins:

Enclosed, please find an information submission to Bone Care's New Drug Application for Hectorol (doxercalciferol) Injection (NDA No. 21-027) which is being submitted as Volume 11.1.

This submission contains the Financial Interests and Arrangements of Clinical Investigators Certification as required in 21 CFR part 54.

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

Sincerely,

Darlene M. Kyllo, Director
Compliance, Quality & Regulatory Affairs

DMK/klb
Enclosure

APPEARS THIS WAY
ON ORIGINAL

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

March 10, 2000

John K. Jenkins, M.D., Acting Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Food and Drug Administration
Center for Drug Evaluation and Research (HFD-510)
Attention: Document Control Room
5600 Fishers Lane
Rockville, MD 20857

RE: NDA No. 21-027 for Hectorol (doxercalciferol) Injection; Volume 10.1

Dear Dr. Jenkins:

Enclosed, please find an information submission to Bone Care's New Drug Application for Hectorol (doxercalciferol) Injection (NDA No. 21-027) which is being submitted as Volume 10.1.

This submission is being sent in response to one follow-up question received in e-mail correspondence from Dr. Eric Colman, dated March 7, 2000.

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

Sincerely,

Darlene M Kyllo

Darlene M. Kyllo, Director
Compliance, Quality & Regulatory Affairs

DMK/klb
Enclosure

APPEARS THIS WAY
ON ORIGINAL

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

PRIVILEGED AND CONFIDENTIAL

March 3, 2000

John K. Jenkins, M.D., Acting Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Food and Drug Administration
Center for Drug Evaluation and Research (HFD-510)
Attention: Document Control Room
5600 Fishers Lane
Rockville, MD 20857

RE: NDA No. 21-027 for Hectorol (doxercalciferol) Injection; Volume 9.1

Dear Dr. Jenkins:

Enclosed, please find an information submission to Bone Care's New Drug Application for Hectorol (doxercalciferol) Injection (NDA No. 21-027) which is being submitted as Volume 9.1.

This submission is being sent in response to comments and information requests received in a letter from Dr. Eric Colman, dated February 28, 2000.

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

Sincerely,

Darlene M. Kyllo

Darlene M. Kyllo, Director
Compliance, Quality & Regulatory Affairs

DMK/klb
Enclosure

APPEARS THIS WAY
ON ORIGINAL

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

February 22, 2000

PRIVILEGED AND CONFIDENTIAL

John K. Jenkins, M.D., Acting Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Food and Drug Administration
Center for Drug Evaluation and Research (HFD-510)
Attention: Document Control Room
5600 Fishers Lane
Rockville, MD 20857

RE: NDA No. 21-027 for Hectorol (doxercalciferol) Injection; Volume 8.1

Dear Dr. Jenkins:

Enclosed, please find an information submission to Bone Care's New Drug Application for Hectorol (doxercalciferol) Injection (NDA No. 21-027) which is being submitted as Volume 8.1.

This submission is being sent in response to comments and information requests received in a letter from Dr. Eric Colman, dated February 18, 2000.

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

Sincerely,

Darlene M Kyllo

Darlene M. Kyllo, Director
Compliance, Quality & Regulatory Affairs

DMK/klb
Enclosure

APPEARS THIS WAY
ON ORIGINAL

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

February 22, 2000

John K. Jenkins, M.D., Acting Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Food and Drug Administration
Center for Drug Evaluation and Research (HFD-510)
Attention: Document Control Room
5600 Fishers Lane
Rockville, MD 20857

PRIVILEGED AND CONFIDENTIAL

RE: NDA No. 21-027 for Hectorol (doxercalciferol) Injection; Volume 7.1

Dear Dr. Jenkins:

Enclosed, please find an information submission to Bone Care's New Drug Application for Hectorol (doxercalciferol) Injection (NDA No. 21-027) which is being submitted as Volume 7.1.

This submission is being sent in response to comments and information requests received in a letter from Dr. Eric Colman, dated February 14, 2000.

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

Sincerely,

Darlene M. Kyllo

Darlene M. Kyllo, Director
Compliance, Quality & Regulatory Affairs

DMK/klb
Enclosure

APPEARS THIS WAY
ON ORIGINAL

Bone Care
INTERNATIONAL
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February 18, 2000

John K. Jenkins, M.D., Acting Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Food and Drug Administration
Center for Drug Evaluation and Research (HFD-510)
Attention: Document Control Room
5600 Fishers Lane
Rockville, MD 20857

RE: NDA No. 21-027 for Hectorol (doxercalciferol) Injection; Volume 7.1

Dear Dr. Jenkins:

Enclosed, please find an information submission to Bone Care's New Drug Application for Hectorol (doxercalciferol) Injection (NDA No. 21-027) which is being submitted as Volume 7.1.

This submission is being sent in response to comments and information requests received in a letter from Dr. Eric Colman, dated February 14, 2000.

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

Sincerely,

Darlene M Kyllo

Darlene M. Kyllo, Director
Compliance, Quality & Regulatory Affairs

DMK/klb
Enclosure

APPEARS THIS WAY
ON ORIGINAL

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

February 17, 2000

PRIVILEGED AND CONFIDENTIAL

John K. Jenkins, M.D., Acting Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Food and Drug Administration
Center for Drug Evaluation and Research (HFD-510)
Attention: Document Control Room
5600 Fishers Lane
Rockville, MD 20857

RE: NDA No. 21-027 for Hectorol (doxercalciferol) Injection; Volume 6.1

Dear Dr. Jenkins:

Enclosed, please find an information submission to Bone Care's New Drug Application for Hectorol (doxercalciferol) Injection (NDA No. 21-027) which is being submitted as Volume 6.1.

This submission is being sent in response to comments and information requests received in a letter from Dr. Duu-Gong Wu, dated February 3, 2000.

Appendix 3 of this submission contains a hard copy and a diskette of the revised package insert which has been updated from that submitted in the NDA (on January 31, 1999, in Volume 1.1, pages 1-6). Revisions that were requested by DMEDP to the proposed package insert for Hectorol Capsules (NDA No. 20-862) between May 7 and June 9, 1999, have been incorporated where they were applicable to the product information for Hectorol Injection. Appendix 3 also contains a redline, strikout version of the package insert, clearly highlighting each of the proposed modifications.

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

Sincerely,

Darlene M. Kyllo, Director
Compliance, Quality & Regulatory Affairs

DMK/klb
Enclosure

APPEARS THIS WAY
ON ORIGINAL

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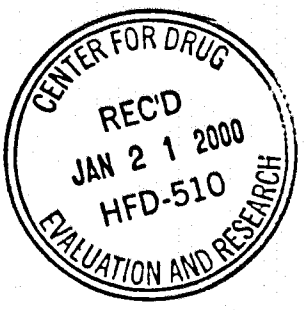
OF COUNSEL
MICHELE F. CROWN
JUR STROBOS, M.D.

DUPLICATE

NDA SUPP AMEND

Jur Strobos, MD
202/518-6377

January 21, 2000



John K. Jenkins, M.D.
Acting Director
Division of Metabolic and Endocrine Drug Products
HFD-510; Parklawn Bldg; Rm. 14B-19
Office of Drug Evaluation II
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Jenkins:

We are in receipt of your January 17 letter with regard to our submission of December 20, 1999, clarifying its status with regard to our new drug application (NDA 21-027) for Hectorol (doxercalciferol) Injection. We respectfully fail to understand the basis for your determination that the submission represents an impermissible major amendment to our application and request reinstatement of our meeting or a response to our previous requests. In particular, we have specifically requested, and were specifically promised, a response to our question with regard to the review of the application under the guidance document, "Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products," which provides for approval based on pharmacological equivalence to other dosage forms of the same active ingredient.

Our discussions with FDA pertaining to Hectorol Injection have focussed on two separate questions: (1) whether the Phase 3 clinical studies were adequately well-controlled or had potentially biased samples, and (2) whether the Division should require two controlled studies for approval of the NDA, or whether pharmacologic equivalence to the oral formulation should be considered in light of the approval of Hectorol Capsules on June 9, 1999 (during the pendency of FDA's consideration of our request for filing over protest).

Regarding the first question above, the medical reviewer suggested in an informal conference on April 9, 1999, that the clinical studies could potentially be biased because of selection of the study population. In our telephone conference of August 24, 1999, the reviewer more clearly illustrated the concern that the patient population gradually decreased from 211 cases initially with Hectorol Capsules, of which 99 were evaluable, to 64 evaluable cases in the subsequent studies supporting Hectorol Injection with patients being gradually eliminated. Even in that telephone conference, however, no evidence of bias in the eliminated cases was shown. Our submission of December 20th merely demonstrates that, in fact, on careful analysis, there was no bias.

The submission contains a further explanation of the patient population flow chart and demonstrates that there were no differences between the initial and final patient populations in terms of iPTH responses to an 8-week washout period. The data for this statistical analysis were all drawn from the application as filed. This statistical analysis was requested by the Division in the August 24 telephone conference to address the question of potential bias. It is not a new analysis of data but merely supports the original analysis as being unbiased in light of the reviewer's concerns. This type of analysis is a common post-submission analysis to address potential concerns raised during review.

Regarding the second question, the Division has never responded either verbally or in writing to the basis for evaluating Hectorol Injection notwithstanding a specific verbal promise this question would be promptly addressed.

Our December 20 submission also addresses this second point. The second part of the December 20 submission contains a further statistical analysis of pharmacokinetic and pharmacodynamic data, all of which data are found in the original filing. This analysis was also requested by the Division to address the issue of pharmacodynamic identity of the two dosage regimens (oral and intravenous) already demonstrated in the filed data. This analysis simply gives more detail to the analysis noted in our letter of September 14, 1999; it also shows where the data originate in the original file, and how the analysis was performed.

Additional ancillary statistical analyses of filed data are frequently requested by the Division, or supplied by sponsors, in light of discussions attendant upon clinical and statistical review. Our submission did not contain new analyses of new data but provided ancillary analyses designed to support the original analyses and to address, for instance, the reviewer's concern about the presence of bias. We are not aware that such clarification would constitute an "amendment" to a file, and we believe upon review you would find it overreaching to consider the December 20 submission as an amendment within the meaning of 21 C.F.R. § 314.60.

Furthermore, we question the premise that an amendment under 21 C.F.R. § 314.60 is prohibited for an application filed over protest. Even if the submission were to represent an amendment, which it is not, the regulation cited in your letter of January 17, 2000, does not support the statement that "an application that is filed over protest is reviewed as submitted, *i.e.*, without further amendment after the new filing date." The cited regulation does state that the agency shall "review [the application] as filed," but the regulation does not state that this review differs in any way from the review of any other application that has been filed without first having been refused. Any other filed application may be amended pursuant to 21 C.F.R. § 314.60 although FDA may consider such a filing an agreement by the sponsor to extend the review period by no more than 180 days.[1]

---

[1] 21 C.F.R. § 314.101(a)(3) provides that, if the applicant requests that FDA file the application, "the agency will file the application over protest under paragraph (a)(2) of this section, notify the applicant in writing, and review it as filed." An application filed and reviewed under (a)(2) is not precluded from the additional filing of a major amendment under 21 C.F.R. § 314.60. To that end, § 314.60(b) carefully specifies the only circumstances in which a filed but not approved application may NOT be amended. This paragraph does not identify applications filed over protest as barring amendment. The Division's apparent reading, that a review as filed means no further amendment is also belied by the fact that § 314.101(a)(3) specifically provides for amendment of an application which has been refused to file as part of the request that FDA file the application and no time limit for that amendment is stated (in contrast to the requirement that the applicant file a request for an informal conference with 30 days). Additionally, the last sentence of § 314.101(a)(3) states that an applicant may also choose to amend the application and resubmit it after which the agency would make a *de novo* assessment of fileability. This provision does not address whether an application that has been filed over protest may also be amended. Any reading of § 314.101(a)(3) that precludes normal handling of an application filed over protest, which includes potential major amendments, would not be consistent with the regulation's express mandate that the application filed over protest be reviewed under FDA's normal procedures.

Finally please note that the Division simply did not provide notification of the filing over protest until October 21 even though there were repeated requests for such notification starting on April 14. Sponsors are precluded from amending an NDA until such notification is received, so this has prevented Bone Care from identifying and providing an appropriate amendment to the file as specifically permitted under §314.101(a)(3). However, as noted above, the December 20 submission is not an amendment since it provides no substantial additional information beyond that provided in the original NDA and merely supplements the correspondence of August 19 and September 14.

We reiterate our request for a meeting to discuss the data in the file as well as to address the outstanding question relating to the standard being used to review the application for Hectorol Injection. Addressing this latter question would also allow Bone Care to develop additional data, if necessary, to address potential deficiencies that might still arise in an office action by the Division. If such concern is unwarranted, we would appreciate being so informed.

We sincerely believe that Hectorol Injection will facilitate and improve the current management of secondary hyperparathyroidism in end stage renal disease patients, especially in patients non-compliant with orally administered therapy. We further believe that cognizant nephrologists would not question the effectiveness and safety of Hectorol Injection were the data contained in NDA 21-027 available for public review.

Please contact me at 202-518-6377 to discuss these issues.

Sincerely yours,

Jur Strobos, MD

JTS:jdc

APPEARS THIS WAY
ON ORIGINAL

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

December 20, 1999

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

RE: NDA No. 21-027, Volume 5.1: Hectorol (doxercalciferol) Injection

Dear Dr. Sobel:

This letter follows from a prior letter, dated September 17, 1999, which Jur Strobos, M.D., our Regulatory Consultant, sent to you on Bone Care's behalf. In that letter, Dr. Strobos requested that DMEDP (1) file the above-referenced NDA over protest according to our written request dated April 14, 1999, and (2) consider a number of proposals from Bone Care intended to facilitate review and approval of this NDA.

We acknowledge and thank you for written notification from DMEDP, dated October 21, 1999, that NDA No. 21-027 was filed in response to our written request of April 14, 1999. Further, we have enclosed a submission (Volume 5.1) which details various elements of the proposals offered in the September 17 letter.

The current submission provides a detailed analysis of the pharmacodynamic and pharmacokinetic data contained in NDA No. 21-027 which demonstrate the therapeutic equivalence of Hectorol Injection and Hectorol Capsules, an approved delivery form of doxercalciferol. We believe that these data supplement our Phase 3 trials of Hectorol Injection and could be used as a basis for approval of Hectorol Injection under the procedures outlined in the Guidance for Industry entitled "Providing Clinical Evidence of Effectiveness for Human Drug and Biologic Products."

The current submission also contains responses to DMEDP's two objections to the Phase 3 trials of Hectorol Injection, as communicated to us by teleconference on July 30, 1999. At that time, the Medical Reviewer expressed concern that the subjects treated in these trials may have been predisposed ("enriched") to positive responses to Hectorol Injection, despite the fact that all available data showed these subjects to be representative of the target population. The Medical

Reviewer's concern was based on a potential selection bias stemming from the small number (n=70) of subjects treated in these trials relative to the original number enrolled (n=211) in the preceding Phase 3 trials of Hectorol Capsules. Further, the Medical Reviewer suggested that the natural course of secondary hyperparathyroidism could be unpredictable in dialysis patients during periods when vitamin D hormone therapy was withheld, such as the 8-week washout periods included in the Phase 3 trials with Hectorol Injection. If this were in fact true, the 8-week washout periods might not be appropriate as historical controls by which the effectiveness of Hectorol Injection could be judged.

Careful analyses by our independent statistical consultants of the Phase 3 data contained in NDA No. 21-027 are delineated in this submission. They show that:

- Bias or enrichment did not occur in the selection of subjects treated with Hectorol Injection, and
- The natural course of secondary hyperparathyroidism is *highly predictable* in dialysis patients during washout from vitamin D hormone therapy.

Bone Care and its independent statistical and regulatory consultants have concluded, therefore, that the 8-week washout periods in the Phase 3 trials with Hectorol Injection can indeed be used as historical control periods by which the effectiveness of this product can be judged.

Bone Care and its statistical and regulatory consultants would like to meet with you to discuss the strength and merit of our conclusion at your earliest convenience.

Sincerely,

Darlene M Kyllo

Darlene M. Kyllo, Director
Compliance, Quality & Regulatory Affairs

DMK/klb

APPEARS THIS WAY
ON ORIGINAL

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

December 1, 1999

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

RE: NDA No. 21-027 for Hectorol (doxercalciferol) Injection; 2 mcg/mL

Dear Dr. Sobel:

Enclosed please find an information amendment to Bone Care International's New Drug Application for Hectorol® (doxercalciferol) Injection. This information is being submitted as Volume 4.1 to NDA No. 21-027 in response to a request for examples of ampule and carton labels.

Included with this submission are draft labels for ampules and cartons to be used with the market packaging of Hectorol® (doxercalciferol) Injection as detailed in NDA No. 21-027.

Also included with this submission is written clarification that the drug substance used in the Hectorol Injection drug product (NDA No. 21-027) is identical to the drug substance used in the Hectorol Capsules drug product (NDA No. 20-862).

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

Best regards,

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

Enclosure

OLSSON, FRANK AND WEEDA, P.C.

ATTORNEYS AT LAW
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OF COUNSEL
MICHELE F. CROWN
JUR STROBOS, M.D.

Jur Strobos, MD
202/518-6377

October 15, 1999

Dr. Solomon Sobel
Director, Division of Metabolic and Endocrine Drug Products
HFD-510; Parklawn Building Rm. 14B-19
Office of Drug Evaluation II
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

By Facsimile – 301-443-9282

Meeting Request
Hectorol® Injection (doxercalciferol)
NDA 21-027

Dear Dr. Sobel:

We understand that a response to our correspondence of September 17, 1999 will be forthcoming from the agency on or about October 22, 1999. This letter requests a meeting with the agency for the afternoon of November 4th (pursuant to our telecon with Randy Hedin, SRMO) to resolve issues that arise from the agency's response. We envision the following agenda:

1. Presentation of Analysis of Comparative Pharmacodynamic Data from the NDA
2. Presentation of Newly Constructed Historical Control and Current Clinical Understanding of Natural History of Secondary Hyperparathyroidism in Renal Failure
3.
4.

We anticipate the following participants:

Charles Bishop, Ph.D.	Bone Care Int'l	CEO
Darlene Kyllo	Bone Care Int'l	Director, Quality, Compliance and Regulatory Affairs
Leon W. LeVan, Ph.D.	Bone Care Int'l	Director, Metabolic and Analytical Chemistry
[redacted]		
Jur Strobos, MD, JD	Consultant	

We might add an additional participant. We would anticipate providing written background materials before the meeting.

Our view is that there is a conceptual disagreement between the Division and Bone Care Int'l on the natural history of untreated secondary hyperparathyroidism over an eight week time course. We are prepared to present empirical data which support our position in order to resolve this controversy.

Thank you for your assistance and please call me at the above-captioned number to finalize these plans.

Sincerely,

Jur Strobos, MD

cc. Randy Hedin

APPEARS THIS WAY
ON ORIGINAL

ORIG AMENDMENT
BM

OLSSON, FRANK AND WEEDA, P.C.
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>HEN D. TERMAN
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ID L. DURKIN
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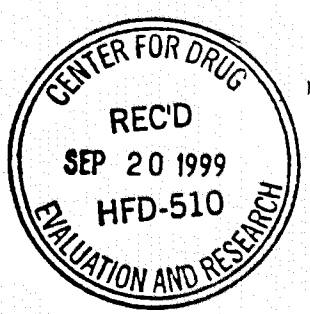
NAOMI J. L. HALPERN
RICHARD D. SIEGEL

OF COUNSEL
MICHELE F. CROWN
JUR STROBOS, M.D.

ORIGINAL



Jur Strobos, MD
202/518-6377

September 17, 1999

Noted & Reviewed with other letters re filing over protest. 10/2/99

UC 151 10/2/99

Solomon Sobel, M.D., Director
Division of Metabolic and Endocrine Drug Products
HFD-510; Parklawn Building Rm. 14B-19
Office of Drug Evaluation II
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Correspondence
Hectorol® Injection (doxercalciferol)
NDA No. 21-027

Dear Dr. Sobel:

This letter, on behalf of our client, Bone Care International ("Bone Care"), proposes a response to the teleconference between DMEDP and Bone Care at 2 p.m. EDT on August 24, 1999, regarding DMEDP's perceived deficiencies in the Phase 3 trials of Hectorol Injection (Clinical Study Nos. H-114-LA and H-114-Memphis) in NDA No. 21-027. These purported deficiencies have precluded the filing of this NDA since they could raise questions about the suitability of the trials as a basis for approving Hectorol Injection. We have attached, at Tab A, a copy of our minutes of this teleconference. We respectfully request a copy of the agency's minutes at your earliest convenience.

We would like to restate our thanks to DMEDP for the opportunity to review the Phase 3 clinical trials conducted with Hectorol Injection. We propose, herein, that DMEDP review NDA No. 21-027 on the basis of pharmacokinetic and pharmacodynamic data which demonstrate the equivalence of Hectorol Injection and Hectorol Capsules. Also, please note that we believe that Bone Care has fully complied with the regulations governing the filing of an NDA over protest following the receipt of a Refuse-to-File ("RTF") letter as set forth in the regulations [21 C.F.R. § 314.101(a)]. We have provided a more detailed explanation of our position at Tab B.

NDA No. 21-027 is an application for marketing approval of an alternative delivery form of an approved active ingredient. As a result, the NDA is entitled to the review procedures outlined in the Guidance for Industry entitled "Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products," which permits the use of pharmacokinetic or pharmacodynamic data to provide substantial evidence of safety and efficacy.

In view of the Guidance for Industry, we propose:

1. ***Comparison of the existing clinical pharmacodynamic data (AUC, t_{max}, iPTH suppression, etc.) of oral versus intravenous doxercalciferol to identify the safe and effective dose for intravenous formulation.*** There are sufficient numbers of patients who have been exposed to oral and intravenous doxercalciferol in clinical studies to permit a meaningful comparison of the two dosage routes even accounting for individual variations. Using data which are in NDA No. 21-027, we will show that the recommended intravenous dose delivers the same activity as the recommended oral dose. We have appended brief graphical presentations of data (at Tabs C and D) contained in the file which illustrate the bioequivalence of the two dosage forms. If this approach is acceptable, we will submit a more complete analysis of the data already in the NDA.

   An example of pharmacokinetic data in this NDA appears in Figure 1 at Tab C. This figure, enclosed with Dr. Bishop's letter to you on September 14, 1999, displays blood levels of 1α,25-dihydroxyvitamin D_2 (the major active metabolite of doxercalciferol) over 48 hours after a 5 μg intravenous or a 5 μg oral dose (oral dose was adjusted by a factor of 0.41 to reflect documented lower bioavailability) in normal subjects. The two formulations are bioequivalent (i.e., the areas under curves are within 20% of each other) although, as expected, t_{max} occurs several hours sooner for the intravenous formulation.

   Examples of pharmacodynamic data in this NDA appear in Figures 2-4 at Tab D. Figures 2 and 3 show that there is equivalence between the dosage forms in the iPTH suppression effected in the identical cohort of patients who were treated first with Hectorol Capsules, during Clinical Study Nos. H-108-LA and H-108-Memphis, and then with Hectorol Injection, during Clinical Study Nos. H-114-LA and H-114-Memphis. Figure 2 shows iPTH suppression in 64 subjects who completed Protocol No. H-114 per protocol and the corresponding iPTH suppression in these same 64 subjects in Protocol No. H-108. Figure 3 shows the corresponding intent-to-treat iPTH suppression in all 70 subjects who were treated in Protocol No. H-114. The iPTH responses to both formulations are indistinguishable ($p = 0.68$) by repeated-measures ANOVA. Figure 4 shows that the iPTH suppression effected by Hectorol Capsules in those 70 subjects is similar to the iPTH suppression effected by Hectorol Capsules in the other 68 subjects who were treated in Clinical Study Nos. H-108 but did not participate subsequently in Clinical Study Nos. H-114. Please note that the significant divergence between the

responses at Weeks 10-12 reflects the effect of discontinuations in the non-continuing group (indicated by the dashed lines).

2. ***Construction of a new historical control for Clinical Study Nos. H-114.*** DMEDP expressed concerns regarding the reliability of the historical controls for Clinical Study Nos. H-114-LA and H-114-Memphis due to the large number of enrolled subjects who were disqualified or discontinued. We propose to construct a more comprehensive historical control. To this end, we have included, at Tab E, copies of the two flowcharts used to illustrate diagrammatically the entry of patients into Clinical Study Nos. H-108 and H-114 which were originally appended to our correspondence dated August 19th. In the initial phase of Clinical Study Nos. H-108, 211 patients entered into an 8-week washout historical control period. We propose to evaluate the time course of plasma iPTH during this washout period in all 211 patients. In the event that iPTH data are not available for all subjects at all timepoints, earlier data will be used instead (in a Last Observation Carried Forward ["LOCF"] approach). This same approach will be taken with a second cohort of 97 patients who entered the later 8-week washout period of Clinical Study Nos. H-114. Following an analysis of poolability, if poolable, these two sets of historical control data which derive from washout in 308 patients will be used to demonstrate the natural history of untreated secondary hyperparathyroidism in this patient population. We believe that, under these conditions, the agency will view this combined historical control as a more useful, clinically relevant comparator by which the effectiveness of intravenous doxercalciferol can be judged. However, in the event that there remains disagreement on this issue, we would request review of this reconstructed historical control during a closed session advisory committee meeting to provide appropriate clinical input. We firmly believe, based on these data and on the opinions of our consultants from within the clinical community, that DMEDP can view the natural history of secondary hyperparathyroidism in patients with renal failure, absent surgical intervention, as consistent and predictable. Additionally, we note that control of iPTH through drug rather than surgical intervention is broadly advocated by leading nephrologists as appropriate state-of-the-art iPTH management in the dialysis population.

3. ***Construction of a new active treatment arm for Clinical Study Nos. H-114.*** While DMEDP has expressed concern about selection bias, we believe that a re-analysis of the existing data from the entire cohort of 70 patients treated with Hectorol Injection using an intent-to-treat analysis (and including drop-outs without available data using an LOCF approach) and the aforementioned historical control should satisfactorily supplement the pharmacodynamic data to support the clinical effectiveness of Hectorol Injection. We propose to include the 4 non-evaluable and 2 discontinuing subjects under the intent-to-treat and LOCF analysis plan. Additionally, and to provide even further support for the absence of selection bias, we propose to analyze (using the LOCF approach) the

effectiveness of Hectorol Injection in the entire cohort of 107 subjects deemed eligible to participate in Clinical Study Nos. H-114 (according to Protocol No. H-114), notwithstanding that 37 of these subjects were not treated.

4. ***Revision of labeling.*** In accordance with our earlier discussions with the Division, we expect that the labeling will have to be revised to correspond to the data and analyses in the NDA as thus amended.

We also propose that we engage in discussions with DMEDP to identify potential Phase 4 studies that would permit the approval of Hectorol Injection as an alternative therapy for dialysis patients with secondary hyperparathyroidism.

We believe that review of NDA No. 21-027 on the basis of the above-referenced Guidance is appropriate, and that our proposals exceed the requirements for approval of Hectorol Injection as an alternative dosage form of an approved active ingredient. We look forward to discussing this different approach to evaluating NDA No. 21-027 with you at your earliest convenience. We will contact your office in the week following the receipt of this correspondence.

Sincerely,

Jur Strobos, MD
Attachments as in text.

APPEARS THIS WAY
ON ORIGINAL

Tab A

This memorandum provides minutes of the teleconference on August 24, 1999, at 2:00 p.m. EDT between the Division of Metabolic and Endocrine Drug Products (DMEDP) of the U.S. Food and Drug Administration (FDA), represented by Drs. Solomon Sobel, Director, Gloria Troendle, Assistant Director, Leo Lutwak, Medical Reviewer, and Todd Sahlroot, Statistical Reviewer, and Maureen Hess, Consumer Safety Officer (substituting for Randy Hedin), and Bone Care International (Bone Care), represented by Dr. Charles Bishop, President, Darlene Kyllo, Director, Regulatory Affairs, and Dr. Jur Strobos, Regulatory Consultant. The conference call ended with the action item that Bone Care would submit a defined proposal for the analysis of the existing New Drug Application for Hectorol Injection (NDA No. 21-027) which Bone Care contended had been filed under protest.

Minutes

Dr. Strobos began the discussion by asking what Bone Care could do to permit completion of review of NDA No. 21-027. Dr. Sobel responded by noting that there was great difficulty in doing so. The reason for not filing the application is that, on its face, the application is unable to support approval. Bone Care will need to run another controlled Phase 3 study, which can be short, with just a few patients, to demonstrate clinical efficacy. He asked whether it might be appropriate to have Dr. Lutwak provide a short summary of DMEDP's rationale. Dr. Strobos agreed, following the bilateral agreement that the conference call could last for until 3:00 p.m.

Dr. Lutwak referred to the flow charts of Bone Care's submission of August 19, 1999, reviewing the course of discontinuations and disqualifications of enrolled subjects from the initial 211 patients enrolled in Clinical Study Nos. H-108 through to the final 64 evaluable patients in Clinical Study Nos. H-114. He was concerned that the 64 patients completing IV treatment might not be representative of the original 211 patients randomized and, under this set of circumstances, he was unsure as to how to evaluate effectiveness. Dr. Bishop noted that Bone Care thought that it had had agency input before initiation of this study as shown by correspondence in the file.

Dr. Strobos asked whether there was any solution to review the NDA. He noted that we were looking at the approval of an intravenous form of an approved active ingredient. Therefore, a solution may be the application of the clinical efficacy guidelines addressing an alternate method of delivery of an approved product, such as use of comparative pharmacokinetic data; re-analysis of Clinical Study Nos. H-114 using existing intent-to-treat data including subjects who dropped out during the washout period; or modification of labeling to provide for use of Hectorol Injection as an alternative to Hectorol Capsules. Dr. Lutwak asserted that his view that a new clinical study was required.

Dr. Sobel advised that, on behalf of the Division, he would like to see these proposals in writing and could not comment on the feasibility of the proposals until he could review them. Dr. Lutwak clarified that the proposal should reference pharmacodynamic (pD) rather than pK data.

Questions were also raised about the reliability of the use of an historical control (wash-out