

NDA 21-027

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

Dear Ms. Kylo:

Please refer to your pending January 31, 1999, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Hectorol (doxercalciferol) Injection.

We are reviewing the clinical section of your submission and have the following comments and information requests:

**H-108 (and H-114) Both Memphis and LA**

1. Please provide an explanation (or speculation) for the increased incidence of hypercalcemia and hyperphosphatemia noted during treatment with oral Hectorol (H-108) vs. treatment with IV Hectorol (H-114).
2. Were any patients in H-108 discontinued from the study because of hypercalcemia or hyperphosphatemia?
3. How many cases of hypercalcemia, hyperphosphatemia, or over-suppression of PTH (<150 pg/ml) occurred in the subjects that did not complete H-108 vs. those subjects that did complete H-108?
4. How many cases of mild hypercalcemia and hyperphosphatemia that resulted in a dosage reduction occurred during the open-label phase of H-114? Please provide these data for the corresponding trial period (first 12 weeks of open-label treatment) in H-108.
5. How many patients were discontinued from H-108 because of lack of efficacy (i.e., inadequate PTH lowering)?
6. What were the mean percent and absolute changes from baseline (Week 0) to Endpoint of the open-label portion of H-08 in levels of PTH for the subjects that did not enter H-114 vs. those that did enter H-114?
7. What were the median weekly doses of drug used during the open-label phase of H-108?
8. For the 42 patients who received open-label treatment in H-114-Memphis and the 28 in H-114-LA, what were the mean absolute changes in 1alpha, 25-(OH)<sub>2</sub>D<sub>2</sub> levels from baseline (Week 0) to Week 12 during open-label treatment in H-108 for these 42 and 28 patients, respectively?

### H-114 Memphis

9. Please provide the following baseline demographic characteristics for the 42 patients who started open-label treatment in H-114: mean serum PTH, Ca, and Phos levels. Please also provide the following baseline demographic characteristics for the 122 subjects who entered the open-label portion of H-108: mean age (range), mean number of months on dialysis, mean PTH level, % male, race (% Caucasian, %Black), and mean serum Ca and Phos levels.
10. In volume 1.9, page 225, third paragraph, it states that 29/40 subjects reached the pre-determined targeted PTH range of 150-300 pg/dl during treatment with Hecatorol. Does this mean on at least one occasion?

### H-114 Los Angeles

11. Please provide the following baseline demographic characteristics for the 28 patients who started open-label treatment in H-114: mean serum PTH, Ca, and Phos levels. Please also provide the following baseline demographic characteristics for the 108 subjects who entered the open-label portion of H-108: mean age (range), mean number of months on dialysis, mean PTH level, % male, race (% Caucasian, %Black), and mean serum Ca and Phos levels.

### H-114 Both Memphis and Los Angeles

12. Please provide the pre-specified primary statistical plan for evaluating efficacy (i.e., lowering of PTH).
13. For those subjects who completed both H-108 and H-114, please compare the correlations between the mean or median cumulative dose of Hecatorol with the mean percent reduction in PTH. The appropriate time period for both studies is baseline (Week 0) to Week 12 of the open-label treatment period.
14. What were the maximum serum calcium and phos levels recorded during the open-label phase?
15. How many subjects had a serum PTH level of < 300 pg/ml on two, three, and greater than 3 consecutive occasions during the open-label treatment period?
16. What were the median weekly doses of Hecatorol used during the open-label phase?

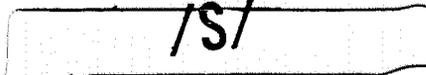
We would appreciate your prompt written response so we can continue our evaluation of your NDA.

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response, as per the user fee reauthorization agreements, we may or may not be able to consider your response prior

to taking an action on your application during this review cycle.

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

Sincerely,

 /S/

Dr. Eric Colman  
Clinical Team Leader  
Division of Metabolic and  
Endocrine Drug Products (HFD-510)  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

APPEARS THIS WAY  
ON ORIGINAL

510/151  
FEB 3 2000

NDA 21-027

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

Dear Ms. Kylo:

Please refer to your January 31, 1999, new drug application for Hectorol (doxercalciferol) Injection.

We also refer to your submission dated December 1, 1999.

Our review of the Chemistry, Manufacturing, and Controls section of your submission including microbiology is complete, and we have identified the following deficiencies:

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We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

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

Sincerely,

/S/ 2-3-00

Duu-Gong Wu, Ph.D.  
Chemistry Team Leader II, for the  
Division of Metabolic and Endocrine Drug Products  
DNDC II, Office of New Drug Chemistry  
Center for Drug Evaluation and Research

APPEARS THIS WAY  
ON ORIGINAL

/S/ 2/3/00

NDA 21-027  
Hectorol IV  
Bone Care International

Date:  
January 27, 2000

CONTACT:  
Ms. Darlene Kylo  
608-236-2530

MEMORANDUM OF TELECON

I spoke with Ms. Darlene Kylo via telephone to discuss the January 21, 2000 letter from Olsson, Frank, and Weeda, P.C. that was sent to us on behalf of Bone Care International. I told her we planned on reviewing the December 20, 1999 submission clarifying Bone Care International's position that Hectorol IV can be approved based on pharmacological equivalence to other dosage forms of the same active ingredient. I further told her that this resolved the issue concerning their request to meet with us, and she agreed.

  
Randy Hedin, PM

APPEARS THIS WAY  
ON ORIGINAL

cc: NDA Arch  
HFD-510/  
HFD-511/RHedin/7.16.99/N21027



NDA 21-027

JAN 17 2000

Food and Drug Administration  
Rockville MD 20857

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

Dear Ms. Kylo:

We acknowledge receipt on December 21, 1999, of your December 20, 1999, correspondence regarding your new drug application for Hectorol (doxercalciferol) Injection. In this document you requested a meeting to discuss the arguments provided in the December 20, 1999, submission. We also refer to the January 5, 2000, telephone conversation between you and Mr. Randy Hedin of this Division in which you agreed to a meeting date of January 25, 2000. However, upon further evaluation of the background material you submitted for this meeting, we have concluded that the meeting is unnecessary. Your December 20 submission constitutes an amendment to your application that was filed over protest. Under the regulation at 21 CFR 314.101(a)(3), an application that is filed over protest is reviewed as submitted, i.e., without further amendment after the new filing date. We apologize for any inconvenience that may have been caused by the cancellation of this meeting.

If you disagree that a meeting is not necessary at this time, we encourage you to discuss the matter with Randy Hedin, R.Ph., Senior Regulatory Management Officer, of this division. If the issue can not be resolved at the combined division/office level, you may formally request reconsideration of the matter at the center level after providing the division an opportunity to review any materials you intend to rely on in an appeal to Murray Lumpkin, M.D., Deputy Director for Review Management, Center for Drug Evaluation and Research. A copy of any appeal should be sent to this division.

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

Sincerely

[Redacted signature area containing the handwritten initials "/S/"]

John K. Jenkins, M.D.  
Acting Director

Division of Metabolic and Endocrine Drug Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

APPEARS THIS WAY  
ON ORIGINAL

OCT 21 1999

NDA 21-027

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

Dear Ms. Kylo:

Please refer to your January 31, 1999, new drug application (NDA) and to the April 6, 1999 informal conference between your representatives and FDA staff concerning our refusal to file your application. This also refers to your April 14, 1999 request that the application be filed over protest.

In response to your request, and in accordance with 21 CFR 314.101(c), the application will be filed over protest.

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

Sincerely,

/S/

10/21/99

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

APPEARS THIS WAY  
ON ORIGINAL

Note to file, there is an error in this letter. The date the informal conference was held is April 9, 1999 (see meeting minutes). The April 6, 1999, date mentioned in this letter is actually the date the meeting was requested.

/S/

21-027

3/01/151

## MEMORANDUM

TO: Solomon Sobel, M.D.

CC: Gloria Troendle, M.D.  
Mr. Durand Hedin

FROM: Leo Lutwak, M.D.

/S/

SUBJECT: Correspondence re NDA 21-027, Hectorol injection, from Jur Strobos, M.D., Dated August 13, 1999.

DATE: September 3, 1999

Dr. Strobos' letter refers to a telephone conference held on August 12, 1999 with participation of those listed above and Dr. Strobos and others representing Bone Care International.

This NDA was submitted on February 1, 1999. After evaluation of the application by the Division, a Refuse-to-File letter was sent to the Sponsor on April 1, 1999. The Sponsor, Bone Care International, discussed the issue raised in a telephone conference on April 9, 1999 and sent a letter re-iterating their position on April 14, 1999. The Agency's position was repeated to the Sponsor in a telephone conference on July 30, 1999. During the telephone conference on August 12, 1999, the Sponsor once again repeated its position and the Agency, once again, responded as before.

In response to Dr. Strobos' comments and suggestions, I would like to emphasize the following:

1. The Sponsor apparently had difficulty carrying out the protocol originally proposed and modified it after initial submission. As a consequence, meaningful statistical analysis cannot be carried out. Protocol modifications must be approved before conduct of the study.
2. Dr. Strobos proposes re-analysis of the submitted data. *Post hoc* analyses cannot be a basis for repair of a failed study. They may be used properly to dredge data for information upon which to design a new study.
3. There are insufficient data to approve a modification of the existing approved label to include any of the observations reported in the material considered in the Refusal-to-File.
4. I urge the Sponsor to prepare a new protocol and submit it for prospective review.

APPEARS THIS WAY  
ON ORIGINAL

NDA 21-027  
Hectorol IV  
Bone Care International

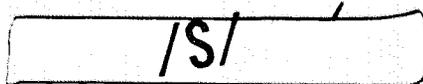
Date:  
July 30, 1999

MEMORANDUM OF TELECON

CONTACT:  
Ms. Darlene Kylo  
Dr. Charles Bishop  
Dr. Jack Coburn  
Dr. Russell Chesney  
608-236-2530

I telephoned Ms. Darlene Kylo; with me were Dr. Sobel, Dr. Lutwak, Dr. Kavanagh, and Dr. Haber, concerning NDA 21-027, Hectorol IV. Dr. Lutwak recapped the deficiencies in the phase 3 clinical trials that led to the refuse to file (see medical officers filing memo). The firm stated that they will address the issues in a written response, and the Division stated it would review the response and reply appropriately.

The Division stated that the design to the right of Hectorol Capsule approved packaging was misleading and should be removed, and the firm stated they would remove it.

  
Randy Hedlin, PM

APPEARS THIS WAY  
ON ORIGINAL

cc: NDA Arch  
HFD-510  
HFD-511/RHedin/8.1.99/N21027

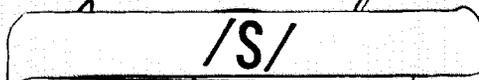
NDA 21-027  
Hectorol IV  
Bone Care International

Date:  
July 16, 1999

CONTACT:  
Ms. Darlene Kylo  
608-236-2530

**MEMORANDUM OF TELECON**

Ms. Darlene Kylo telephoned me to discuss the Hectorol IV refuse-to-file status. I told her the status of the application is refuse-to-file as stated in our letter dated on, April 1, 1999. I informed Ms. Kylo that the reasons for the refuse-to-file status are described in the letter of April 1, 1999, and if she wants further clarification she should send a letter to the Division. She stated that she would.

A rectangular box containing the handwritten initials "/S/".

Randy Hedra, PM

**APPEARS THIS WAY  
ON ORIGINAL**

cc: NDA Arch  
HFD-510/  
HFD-511/RHedin/7.16.99/N21027

NDA 21-027

APR 1 1999

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

Dear Ms. Kylo:

Please refer to your January 31, 1999, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Hectorol (doxercalciferol) Injection.

We have given your application a preliminary review, and we find it is not sufficiently complete to merit review. Thus, it will not be filed as a new drug application within the meaning of section 505(b) of the Act.

We are refusing to file this application under 21 CFR 314.101(d) for the following reasons:

1. The application is incomplete because it does not on its face contain information required under section 505(b) in that it does not contain adequately controlled clinical trials. The original protocol was designed to have the subjects in the injectable doxercalciferol study serve as their own controls after having been treated with either a placebo or an oral doxercalciferol. However, patients were switched from placebo or oral doxercalciferol to oral or parenteral calcitriol for variable periods up to six months before the intravenous doxercalciferol formulation became available for the study. Because the only endpoint measured was PTH (as there is no valid assay to discriminate between the drug doxercalciferol and the active metabolite), there is no way to distinguish between the effect of calcitriol versus doxercalciferol. Thus, the study did not have a valid control against which to evaluate the efficacy of Hectorol Injection.
2. The application is incomplete because it does not contain the required information on plasma drug/metabolite levels at clinically relevant doses, and it does not qualify for a waiver.

Within 30 days of the date of this letter, you may request in writing an informal conference about our refusal to file this application. To file this application over FDA's protest, you must avail yourself of this informal conference. We encourage you to discuss the design of any additional studies prior to their initiation.

If after the informal conference, you still do not agree with our conclusions, you may make a written request to file the application over protest, as authorized by 21 CFR 314.101(a)(3). If you do so, this application shall be filed over protest under 21 CFR 314.101(a)(2). The filing date will be 60 days after the date you requested the informal conference.

FDA will refund 75% of the user fee submitted with the application. If you decide to file this application over protest, the filing of this application over protest will be regarded by the Agency as a new original application for user fee purposes, and will be assessed a user fee applicable to a new submission.

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

Sincerely,

*[Handwritten signature box containing "/S/"]*

*4/11/99*

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

cc:

Archival NDA 21-027  
HFD-510/Div. Files  
HFD-510/R.Hedin  
HFD-510/Reviewers and Team Leaders  
HFD-95/DDMS  
HFD-820/DNDC Division Director  
DISTRICT OFFICE

Drafted by: RH/March 22, 1999

Initialed by: RKavanagh/3.22/LLutwak/3.24/GTroendle/HAhn/TSahlroot/JRhee for EGalliers/3.25.99

Revised by: EGalliers/3.30.99/4.1.99/

Initialed by: LLutwak/3.31/HAhn/GTroendle/4.1.99/

final: EGalliers/4.1.99/

filename: \_\_\_\_\_

*4.1.99*  
*[Handwritten signature box containing "/S/"]*

REFUSAL TO FILE (RF)

510/ [SI]

NDA 21-027  
Hectorol (doxercalciferol) Injection  
Bone Care International

Date:  
4/1/99

CONTACT:  
Ms. Darlene Kylo  
608-236-2500

MEMORANDUM OF TELECON

I spoke with Ms Kylo, concerning the refuse-to-file letter that we are sending her firm. She asked if I would fax a copy of the letter to her and I stated that I would. She also stated that the firm would like to meet with us as soon as possible, and I stated that I would set up a meeting.

[Redacted signature box with handwritten 'SI']  
Randy Hedra, CSO

APPEARS THIS WAY  
ON ORIGINAL

cc:NDA Arch  
HFD-510  
HFD-511/RHedin/4.1.99/N21027

FEB 8 1999

NDA 21-027

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

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 (doxercalciferol) Injection, 2 mcg/mL

Therapeutic Classification: Standard (S)

Date of Application: January 31, 1999

Date of Receipt: February 2, 1999

Our Reference Number: 21-027

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on April 3, 1999, in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be December 2, 1999, and the secondary user fee goal date will be February 2, 2000.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal/Courier/Overnight Mail:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Metabolic and Endocrine Drug Products, HFD-510  
Attention: Division Document Room  
5600 Fishers Lane  
Rockville, Maryland 20857

NDA 21-027

Page 2

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

Sincerely yours,

131 25.99

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

cc:

Archival NDA 21-027  
HFD-510/Div. Files  
HFD-510/R.Hedin  
HFD-510/TeamLeaders  
DISTRICT OFFICE

Drafted by: emg/February 5, 1999

final:emg

filename: \_\_\_\_\_

ACKNOWLEDGEMENT (AC)

APPEARS THIS WAY  
ON ORIGINAL

# Bone Care

INTERNATIONAL

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

March 29, 2000

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

RE: Revised draft labeling for Hectorol Injection (doxercalciferol)

Dear Dr. Jenkins:

Pursuant to my telephone conversation with Randy Hedin earlier today, we have prepared and attached a revised copy of the draft labeling for Hectorol Injection. The revised labeling contains the following modifications suggested by DMEDP:

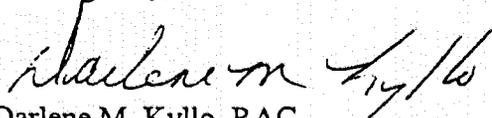
1. On page one, the content of disodium edetate per milliliter of solution has been corrected from  mg to 1.1 mg.
2. On pages 3 and 4, the efficacy data has been revised to include all 70 patients treated with Hectorol Injection instead of only the .
3. On page 10, the two sentences regarding  the Hectorol Injection solution have been deleted.

We also have added the Bone Care identification code information and anticipated publication date to the end of the document.

Additions and deletions are identified by using bold type and strike-outs, respectively. A clean copy without the bold and strike-out fonts also is included.

I can be reached at (608) 236-2530 if you have any questions.

Best regards,



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

Enclosure

**APPEARS THIS WAY  
ON ORIGINAL**

15 Page(s) Redacted

# Bone Care

INTERNATIONAL

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

March 23, 2000

John K. Jenkins, M.D., Acting Director  
Division of Metabolism and Endocrine Drug Products  
Office of Drug Evaluation II  
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. 21-027 for Hectorol Injection (doxercalciferol)

Dear Dr. Jenkins:

I am writing to inform you that Bone Care's contract labeler and secondary packager, [redacted] is now ready to provide vial labeling and packaging operations for Hectorol Injection in support of NDA No. 21-027. A letter from [redacted] confirming their readiness status is attached.

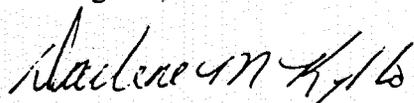
[redacted] located in [redacted] was not ready for a pre-approval inspection in support of NDA No. 21-027 when inspected by the [redacted] District FDA between December 15 - 22, 1999, due to a miscommunication between Bone Care and [redacted]. A copy of the Form FDA 483 issued to [redacted] is attached.

The process of labeling and packaging the ampules at [redacted] is a manual operation. As such, no validation of the equipment performance can be conducted as with an automated or semi-automated process. Instead, a 100% QC inspection will be performed on all units. A copy of the Hectorol Injection Drug Product Quality Manual for the labeling and packaging process at [redacted] is attached.

We have contacted the [redacted] District FDA and informed the Director of Investigations that [redacted] is now ready for re-inspection. We are hopeful that the District can complete its re-inspection prior to the user's fee goal date; however, in the event that this is not possible, we hope that you will conclude that this is not a substantive issue given that this is a manual operation and that [redacted] has an irreproachable record for cGMP processing operations.

I can be reached at (608) 236-2530 if you have any questions.

Best regards,



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

APPEARS THIS WAY  
ON ORIGINAL

Enclosures

ORIGINAL

Bone Care  
INTERNATIONAL

NDA SUPP AMEND  
N-SU

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

March 20, 2000



John K. Jenkins, M.D., Acting Director  
Division of Metabolism and Endocrine Drug Products  
Office of Drug Evaluation II  
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. 21-027 for Hectorol (Doxercalciferol) Injection: Safety Update

Dear Dr. Jenkins:

Enclosed, please find a submission to Bone Care's New Drug Application for doxercalciferol (Hectorol; 1-alpha-hydroxyvitamin D<sub>2</sub>) 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 February 11, 1998 (the cut-off date for information included in Volume 1 of NDA No. 21-027) through March 1, 2000.

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

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

# Bone Care

INTERNATIONAL

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

March 17, 2000

John K. Jenkins, M.D., Acting Director  
Division of Metabolism and Endocrine Drug Products  
Office of Drug Evaluation II  
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. 21-027 for Hectorol Injection (doxercalciferol), Volume 12.1

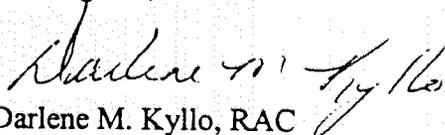
Dear Dr. Jenkins:

Enclosed please find revised draft labeling for Hectorol Injection in response to DMEDP's comments which Randy Hedin emailed to me on Friday, March 10, 2000. This revision has incorporated most of the Division's comments and suggestions. This is being submitted at Volume 12.1 to NDA No. 21-027.

Additions and deletions are identified by using bold type and strike-outs, respectively; comments are in brackets.

I can be reached at (608) 236-2530 if you have any questions.

Best regards,



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

Enclosure

APPEARS THIS WAY  
ON ORIGINAL