DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-862/S-006

Bone Care International
Attention: R. Andrew Morgan, R.Ph.
Vice President, Compliance, Quality & Regulatory Affairs
1600 Aspen Commons
Middleton, WI 53562

Dear Mr. Morgan:

Please refer to your supplemental new drug application dated December 22, 2001, received December 27, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Hectorol (doxercalciferol) Capsules.

We acknowledge receipt of your submissions dated October 31, 2002, and January 24, March 26, June 3, October 23, November 25, 2003, and March 30 and April 7, 15, 20, 21, 22(2), and 23(3), 2004.

Your submission of October 23, 2003, constituted a complete response to our October 25, 2002, action letter.

This supplemental new drug application proposes the use of a new, lower strength of Hectorol Capsules, (0.5 ug), for the management of secondary hyperparathyroidism in patients with moderate to severe chronic renal insufficiency not yet on dialysis.

We completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text and with the minor editorial change to the containers and cartons which will be implemented after manufacture of Lot no. 003. The editorial change is listed below.

- The dosage form name "Capsules" must follow the established name on the container labels and cartons.

The final printed labeling (FPL) must be identical to the enclosed labeling (package insert) and include the minor editorial revision to the submitted labeling (immediate container and carton labels submitted April 22, 2004). We remind you of your commitment to make a minor labeling change to the containers and cartons after production of Lot no. 003. This change can be submitted as a CBE-0 labeling supplement, which must contain final printed labeling.

Please submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – NDAs*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount 15 of the copies on heavy-weight paper or similar material. For administrative

purposes, this submission should be designated "FPL for approved supplement NDA 20-862/S-006". Approval of this submission by FDA is not required before the labeling is used.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are waiving the pediatric study requirement for ages 0 to 4 years and deferring pediatric studies for ages 5 to 18 years for this application.

Your deferred pediatric studies required under section 2 of the Pediatric Research Equity Act (PREA) are considered required postmarketing study commitments. The status of this postmarketing study shall be reported annually according to 21 CFR 314.81. This commitment is listed below.

1. Deferred pediatric study under PREA for the management of secondary hyperparathyroidism in pediatric patients ages 5 to 18 years with Stage 3 or 4 chronic kidney disease (CKD) not yet on dialysis.

   Final Report Submission: April 2006

Submit final study reports to this NDA. For administrative purposes, all submissions related to this pediatric postmarketing study commitment must be clearly designated "**Required Pediatric Study Commitment**".

We also remind you of your additional postmarketing study commitments in your submissions dated April 15 and 21, 2004. These commitments are listed below.

1. To conduct a two year carcinogenicity study in a single species.

Protocol Submission:	by November 2004
Study Start:	by February 2005
Final Report Submission:	by June 2008

2. To conduct a clinical trial designed to address recommendations made in the National Kidney Foundation K/DOQI guidelines regarding safety and efficacy of doxercalciferol in lowering elevated iPTH to within accepted ranges in "vitamin D sufficient" patients with Stages 3 and 4 chronic kidney disease (CKD).

Protocol Submission:	by September 2004
Study Start:	by January 2005
Final Report Submission:	by February 2007

In addition, we remind you of your April 22, 2004, submission agreeing to tighten the acceptance limits for strength from(b)(4)----------of label claim. This change should be made for both strengths of Hectorol ca----------nd 2.5 µg. Since a tighter assay specification is expected to provide for a greater quality assurance, this change may be submitted as a CBE-0 supplement to the original NDA within six months.

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21

CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "**Postmarketing Study Protocol**", "**Postmarketing Study Final Report**", or "**Postmarketing Study Correspondence**."

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Pat Madara, Regulatory Project Manager, at (301)827-6416.

Sincerely,

{See appended electronic signature page}

David G. Orloff, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Eric Colman
4/23/04 05:42:08 PM
Eric Colman for David Orloff