CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-027

CORRESPONDENCE

. 510 / /S/

JAN 27 1999

CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
Carol Holquist, Safety Evaluator
(OPDRA; HFD-400)

DATE RECEIVED:	**DUE DATE:**	**OPDRA CONSULT #:** 99-106
December 14, 2000	January 31, 2000	

TO (Division):
John Jenkins, MD
Acting Director, Division of Metabolic and Endocrine Drug Products
HFD-510

PRODUCT NAME:	**MANUFACTURER:**
Hectorol (Doxercalciferol Injection) **NDA #:** 21-027	Bone Care International

OPDRA RECOMMENDATION:

OPDRA has no objections to the continued use of the proprietary name Hectorol for this injectable product. OPDRA considers this a final review due to the primary goal date of 31 January 2000.

/S/ 1/21/2000

Jerry Phillips
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3246
Fax: (301) 480-8173

/S/ 1/27/00

Peter Honig, MD
Deputy Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

APPEARS THIS WAY
ON ORIGINAL

Office of Post-Marketing Drug Risk Assessment
HFD-400; Rm. 15B03
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: January 18, 2000

NDA# 21-027

NAME OF DRUG: Hectorol (Doxercalciferol Injection)

NDA HOLDER: Bone Care International

I. INTRODUCTION:

This consult was written in response to a request from the Division of Metabolic and Endocrine Drug Products (HFD-510) to review the proposed proprietary drug name, Hectorol, regarding potential name confusion with existing proprietary/generic drug names.

Only portions of the container labels, carton and insert labeling were available for review and comment.

PRODUCT INFORMATION

Hectorol is a synthetic vitamin D pro-drug for 1∝,25-dihydroxyvitamin D_2, a naturally occurring active form of vitamin D_2. Vitamin D2 and D3 must be metabolically activated in the liver and kidney before becoming fully active on target tissues. Hectorol is available as a sterile, clear, colorless solution for intravenous injection. Each mL of solution contains 2 mcg of doxercalciferol. Hectorol is indicated for the reduction of elevated iPTH levels in the management of secondary hyperparathyroidism in patients undergoing chronic renal dialysis. The recommended initial dose of Hectorol is 4 mcg administered as a bolus dose three times weekly at the end of dialysis, or approximately every other day. The initial dose should be adjusted, as needed, in order to lower blood PTH into the range of 150 to 300 pg/mL. The dose may be increased at 8 week intervals by 1 to 2 mcg if PTH is not lowered by 50% and fails to reach the target range. Hectorol will be supplied as a 2 mcg/mL solution available in 1 mL and 2 mL amber glass ampules.

Hectorol is also available in a capsule formulation under NDA 20-862. This NDA was approved on June 9, 1999. Each capsule contains 2.5 mcg of doxercalciferol. The dosing varies between the capsule and injection formulations. The capsule has a recommended initial dose of 10 mcg administered three times weekly at dialysis, approximately every other day. The dose may be increased at 8 week intervals by 2.5 mcg and the maximum recommended dose of Hectorol is 20 mcg administered three times a week at dialysis for a total of 60 mcg per week.

II. RISK ASSESSMENT:

In order to predict the potential for medication errors and to determine the degree of confusion associated with the proposed name, Hectorol, with other approved and unapproved drug names, the medication error staff of OPDRA searched ALTMEDDEX Intranet Series, 1999, which includes the following published texts: DrugDex, Poisindex, Martindale, RPS Herbal Medicines, Index Nominum, and Physicians' Desk Reference (1999). Additional publications utilized to search for potential sound-alike or look-alike names to approved drugs were the American Drug Index (43rd Edition), Drug Facts and Comparisons (Updated Monthly), the Electronic Orange Book, CDER's New Approvals, and the US Patent and Trademark Office online database. OPDRA also searched several FDA databases for potential sound-alike or look-alike names to unapproved/approved drugs (Establishment Evaluation System (EES), Drug Product Reference File (DPR), Decision Support System (DSS) and the LNC database). In addition, OPDRA conducted an internal study of written and verbal analysis of the proposed proprietary name, involving health care practitioners within FDA, to evaluate potential errors in handwriting and verbal communication of the name. This exercise was conducted to simulate an actual practice setting. Lastly, a search was conducted in AERS to determine if there has been any medication error reports associated with confusion of the proprietary name Hectorol.

A. STUDY CONDUCTED BY OPDRA

Methodology:

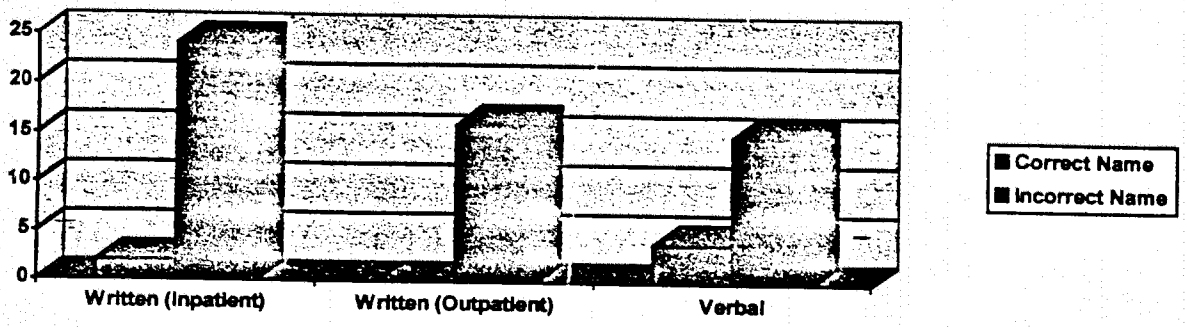
The Hectorol studies involved 92 health professionals, comprised of pharmacists, physicians, and nurses within FDA, to determine the degree of confusion of Hectorol with other drug names due to the similarity in handwriting and verbal pronunciation of the name. OPDRA staff members wrote one inpatient order and four outpatient prescriptions, each consisting of unknown drug products in addition to a prescription for Hectorol (see below). These prescriptions were scanned into the computer and a random sample of the written orders, were then delivered to the participating health professionals via e-mail. In addition, one pharmacist recorded the outpatient orders on voice mail. The voice mail messages were then sent to the participating health professionals for their review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Outpatient RX: Hectorol UD 30 day supply	Give Hectorol as directed, 30 day supply, with no refills
Inpatient RX: Start Hectorol 4 mcg 3 x week UD	

APPEARS THIS WAY
ON ORIGINAL

Results:

We received responses from sixty-one out of ninety-two participants (66%), six of which interpreted the name correctly. Sixteen participants interpreted outpatient prescription orders, twenty-six interpreted inpatient orders, and nineteen interpreted verbal orders. The results are as follows:



percent of the participants interpreted the name correctly. All outpatient prescriptions were interpreted incorrectly. One of the participants volunteered that if this was a rectal product the "K" could be taken as an "R". The remaining responded with the following incorrect interpretations:

Verbal		Written	
Hectoral	Hecterol	Kectoral	Kerctoral
Hectrol	Hectetrol	Keutoral	Rectoral
Hecteral	Hectoril	Lectoral	Kenteral
		Hectoral	Hwctoral
		Herteral	

B. FOCUS GROUP FINDINGS

The group identified and discussed the following sound-alike/look-alike drug names (Hexadrol, Habitrol, Helicosol and Ketorolac).

Product Name	Dosage form(s), Generic name	Usual dose*	Other
Hectorol	Injection, Oral Capsule Doxercalciferol	Injection - 4 mcg administered as a bolus dose three times weekly at the end of dialysis, or approximately every other day. Capsule - 10 mcg administered three times weekly at dialysis, approximately every other day.	
Hexadrol	Tablet Dexamethasone 4 mg	0.75 mg to 9 mg daily	S/A (look-alike) per OPDRA.

Product Name	Dosage form(s), Generic name	Usual dose*	Other
Hectorol	Injection, Oral Capsule Doxercalciferol	Injection - 4 mcg administered as a bolus dose three times weekly at the end of dialysis, or approximately every other day. Capsule - 10 mcg administered three times weekly at dialysis, approximately every other day.	
Habitrol	Transdermal Patch Nicotine 7 mg/24 hr, 14 mg/24 hr and 21 mg/24hr	One 21 mg patch daily for 4 to 8 weeks then one 14 mg patch for 2 to 4 weeks then one 7 mg patch daily for 2 to 4 weeks then DC.	S/A per OPDRA
Helicosol	Diagnostic drug – Powder for reconstitution	30 minutes before blood test	L/A per OPDRA
Ketorolac	10 mg Tablet, 15 mg/mL and 30 mg/mL Injection and 0.5% Ophthalmic solution Ketorolac tromethamine	Opth.-1 drop 4 times daily. Inj.-30 mg IM q 6h Tab-1 q4-6h max 40 mg	L/A per OPDRA

After discussion, the group determined the names identified above had a low potential for confusion with Hectorol when written and spoken and thus did not pose a significant safety risk.

C. DISCUSSION:

The results of the verbal and written analysis studies demonstrate six out of sixty-one participants interpreted the proprietary name correctly. We recognize that low scores of correct interpretations would be common for all unapproved drug product names because health professionals are not familiar with the name. Although hectorol has been on the market since June of 1999, it is only utilized in dialysis patients. This could account for the unfamiliarity of the name among the participants. The majority of respondents provided misspelled variations of the drug name but these responses generally were phonetic variations of the name. The inaccurate interpretations of the proposed name did not overlap with any existing approved drug products. The proprietary name does not contain any USAN stems. In addition, the searches conducted within OPDRA did not uncover any additional names that were not discussed within the focus group. Lastly, the AERS search did not uncover any existing problems associated with medication errors due to the name.

III. LABELING, PACKAGING AND SAFETY RELATED ISSUES

A. CONTAINER (2 mcg x 1 mL and 4 mcg x 2 mL ampules)

1. As noted in the USP (General Notices; pg. 13) the abbreviation "mcg" is commonly employed in labeling and prescription writing. Based on our post-marketing experience OPDRA would also recommend that "mcg" be used instead of "μg" to denote micrograms.

2. In accordance with the General Notices (pg. 12) of the 1995 USP, "in order to minimize the possibility of errors in the dispensing and administration of drugs, the quantity of active ingredient when expressed in whole numbers shall be shown WITHOUT a decimal point that is followed by a terminal zero." The terminal zero in "2.0 mcg and 1.0 mL" should be deleted to avoid a tenfold confusion on strengths. In addition, the carton and insert labeling should be revised accordingly.

3. The would recommend that the total drug content be included in the expression of strength of an injectable drug product within this volume range. We offer the following recommendations:

   a. 1 mL ampule:

      2 mcg/mL

   b. 2 mL ampule:

      4 mcg/2 mL
      (2 mcg/mL)

APPEARS THIS WAY
ON ORIGINAL

4. We note that the established name for this product is incorrect (see USP – General Chapter <1>). Since this is an injectable solution the established name should be:

   (Doxercalciferol Injection)

B. CARTON (100 x 1 mL and 100 x 2 mL)

1. See comments under CONTAINER.

2. Decrease the prominence of "100". The 100 appears larger and more prominent that the product strength. The size of the net quantity statement should not distract from the most important components of the labeling, the name and strength of the product. We would recommend that the net quantity be relocated to the bottom of the main display panel with less prominence.

C. INSERT

DOSAGE AND ADMINISTRATION – Paragraph two:

Delete the terminal zeros that appear in conjunction with the product strength for the reason outlined above (4 mcg, 1-2 mcg and 1 mcg).

IV. RECOMMENDATIONS:

A. OPDRA has no objections to the continued use of the proprietary name Hectorol for this injectable product.

B. OPDRA recommends the above labeling revisions to encourage the safest possible use of this product.

C. OPDRA considers this a final review due to the primary goal date of 31 January 2000.

If you have further questions or need clarifications, please contact Carol Holquist at 301-827-3244.

/S/ 1/21/2000
Carol Holquist, RPh
Safety Evaluator
Office of Post-Marketing Drug Risk Assessment

Concur:

/S/ 1/21/2000
Jerry Phillips, RPh
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment

APPEARS THIS WAY
ON ORIGINAL

Electronic Mail Message

Date: 3/29/00 4:46:40 PM
From: Martin Haber (HABERM)
To: Randy Hedin (HEDINR)
To: Duu Gong Wu (WUD)
Subject: FWD: Overall OC Recommendation NDA 21027/000

labeler is now acceptable, overall EER status is now acceptable for Hectorol IV

martin

APPEARS THIS WAY
ON ORIGINAL

Electronic Mail Message

Date: 3/30/00 9:20:03 AM
From: Bryan Riley (RILEYB)
To: Randy Hedin (HEDINR)
Subject: NDA 21-027

Randy,

I've finished my review of the amendment to this NDA and have recommended for approval. My review is in DFS.

Bryan

APPEARS THIS WAY
ON ORIGINAL

/S/ 11/1-99

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO (*Division/Office*) HFD-160 Attn: Peter Cooney		FROM: HFD-510	
DATE: November 1, 1999	IND NO.	NDA NO. 21-027	TYPE OF DOCUMENT N	DATE OF DOCUMENT January 31, 1999
NAME OF DRUG Hectorol IV		PRIORITY CONSIDERATION S	CLASSIFICATION OF DRUG 3S	DESIRED COMPLETION DATE January 1, 1999
NAME OF FIRM Bone Care International				

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- MANUFACTURINGCHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW	☐ CHEMISTRY REVIEW
☐ END OF PHASE II MEETING	☐ PHARMACOLOGY
☐ CONTROLLED STUDIES	☐ BIOPHARMACEUTICS
☐ PROTOCOL REVIEW	☐ OTHER
☐ OTHER	

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS *(List below)*
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: Please review the attached microbiology section of a new NDA submitted by Bone Care International.
Dr. Martin Haber is the reviewing chemist, 827-6388.
Mr. Randy Hedin is the CSO, 827-6382.

SIGNATURE OF REQUESTER /S/	METHOD OF DELIVERY *(Check one)* ☒X MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

Consult.080

To Riley
11-17-99
/S/

CENTER FOR DRUG
REC'D
NOV 2 1999
HFD-160
EVALUATION AND RESEARCH

Meeting Date: August 24, 1999 Time: 2:00 p.m. – 3:00 p.m. Location: Dr. Sobel's office

NDA 21-027 Hectorol (doxercalciferol)

Type of Meeting: Teleconference

Meeting Chair: Dr. Solomon Sobel

Meeting Recorder: Ms. Maureen Hess

External participant lead: Dr. Charlie Bishop

FDA attendees and titles:

Dr. Solomon Sobel	Director, DMEDP
Dr. Gloria Troendle	Deputy Director, DMEDP
Ms. Maureen Hess	CSO, DMEDP
Dr. Leo Lutwak	Medical Officer, DMEDP
Dr. Todd Sahlroot	Team Leader, Biostatistics

External participant and titles:

Dr. Strobos	Bone Care International, Consultant
Dr. Charlie Bishop	Bone Care International
Ms. Darlene Kyllo	Bone Care International

Meeting Objectives:

Meeting requested by FDA to discuss the August 19, 1999 fax submitted by the sponsor.

Discussion Points:

- The Division stated that after reviewing the August 19, 1999 fax submission by the sponsor it believes that it is still unable to file the application. The study is unable to support approval. The Division referred to the first flow chart of the 8/19/99 fax. The Division stated that at the end of the study, there were only 64 patients who were evaluable. Those 64 patients are not representative of the population randomized, making it difficult to evaluate the data and their meaning.

- The sponsor stated that it understands the concept that of the original 211 patients, only 64 are evaluable patients, but the application is for an alternate dosage form of an approved active ingredient. The sponsor stated that using the current guidance documents, it is hoping to use the current study and/or a pharmacokinetic study (PK). The sponsor added that it is amenable to different proposals. The Division stated that it still will not have anything that adds up to evaluable use of the drug. The Division added that it would like to see a properly randomized and controlled study, one that is well-designed that shows what the intravenous form does or does not do. The Division added that the study could be relatively short. The

Division stated that it is unclear about the sponsor's proposal of a PK study, because there have been no PK studies done, perhaps the sponsor means a pharmacodynamics study. The Division requested that the sponsor put their proposals in writing.

- The sponsor inquired if they could use the oral study as historical data. The Division replied negatively. The sponsor inquired about labeling that advises on converting patients from oral administration to intravenous administration. The Division replied that if the study had been conducted as originally designed, then that would be conceivable, but this is not the case. The sponsor stated that the mean values of hyperparathyroidism clearly show the effect of the drug and the reason for the complex design of the study was to prevent the patient from being on placebo for an extended period of time without worsening their disease. The Division replied that the means alone are not sufficient, that the variability also needs to be estimated. The Division inquired about what the sponsor proposes to compare. The sponsor stated that the comparison would be washout to treated population. The Division commented that the proposed comparison is lacking a control and a control group is needed. The sponsor stated that it understands the Division's concerns but added that most patients received Rocaltrol.

- The sponsor proposed filing with a commitment to obtain the requested information. The Division stated that it does not see how it can use the current data to file the application. The Division added that a new study with PD data might be a better approach. However, the Division will consider the sponsor's proposals and requested the sponsor to submit those proposals in writing. The sponsor agreed to do so.

- The sponsor stated that they officially filed the application over protest, but have not received any response from the Agency. The Division stated that it is not aware of any such filing and inquired as to the date of the submission. The sponsor stated this was done April 14, 1999. The Division reiterated that it is unaware of any such action by the sponsor, but will look into it.

Decisions (agreements) reached:

- Sponsor will submit their proposals in writing.

- Division will investigate the sponsor's claim that the application has been filed over protest.

Minutes preparer, Maureen Hess, MPH, RD /S/

Chair, Solomon Sobel, MD /S/

Concurrence: TSahlroot/10.8.99/LLutwak/10.8.99/GTroendle/10.12.99/SSobel/10.14.99

Meeting Date: April 9, 1999 Time: 2:30 - 4:00 PM Location: 14-56

NDA 21-027 Hectorol IV(1-alpha-hydroxyvitamin D_2)

Type of Meeting: General Meeting

External participant: Bone Care International

Meeting Chair: Dr. Gloria Troendle

External participant lead: Ms. Darlene Kyllo

Meeting Recorder: Mr. Randy Hedin

FDA Attendees and titles:

Dr. Solomon Sobel, Director, DMEDP
Dr. Gloria Troendle, Deputy Director, DMEDP
Dr. Leo Lutwak, Medical Reviewer DMEDP
Dr. Gemma Kuijpers, Pharmacology Reviewer, DMEDP
Dr. Ronald Kavanagh, Reviewer, OCPB
Dr. Hae-Young Ahn, Team Leader, OCPB
Mr. Randy Hedin, CSO, DMEDP

External participant Attendees and titles:

Dr. Charles W. Bishop, President
Ms. Darlene Kyllo, Director, Regulatory Affairs
Dr. Jack Coburn, Consultant
Dr. Russell Chesney, Consultant
Dr. Dick Margess, Consultant

Meeting Objectives:

This meeting was requested by Bone Care International to discuss the refuse-to-file letter, and how to address the deficiencies cited in the letter.

Discussion Points and Decisions (agreements) reached:

- Dr. Bishop provided background information leading up to the refuse-to-file letter.
- The Division stated that the firm did not follow the protocol that was submitted. 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, and a statistical review cannot be done.

- The Division stated that the study was not a crossover study as the subtitle of Protocol H-114 stated. The firm stated that this term was a misnomer in that the trial was never envisioned to be conducted as a true crossover trial. The firm stated that the trial involved only patients who had participated in studies previously completed under Protocol H-108 and incorporated historical controls as stated in the proposed analysis, final reports, and in the NDA. However, the Division stated that the firm did not follow the Division's advise to do a crossover trial, and the lack of adequate controls makes the trial inadequate. The Division further stated that doing a crossover trial would have allowed a comparison of the two groups.

- The firm stated it will submit a detailed response in writing to the Division's concerns, and the Division replied that it will review this response.

Unresolved or issues requiring further discussion:

- None

Action Items:

- The firm will submit a written response to the Division's concerns.

Signature, minutes preparer: /S/

Concurrence Chair: /S/

cc: NDA Arch
HFD-510
Attendees
HFD-510/EGalliers
HFD-511/RHedin/4.13.99/N21027.MN2

Concurrences: LLutwak/RKavanagh/12.15/CTroendle/12.16/GKuijpers/HAhn/SSobel/12.21/

Meeting Date: March 17, 1999 Time: 10:30 - 11:30 pm Location: 14-56

NDA 21-027 Hectorol (1-alpha-hydroxyvitamin D_2) IV

Type of Meeting: Filing Meeting

External participant: None

Meeting Chair: Dr. Troendle

External participant lead: None

Meeting Recorder: Mr. Randy Hedin

FDA Attendees and titles:

Dr. Solomon Sobel, Division Director, DMEDP
Dr. Gloria Troendle, Deputy Division Director, DMEDP
Dr. Leo Lutwak, Medical Reviewer, DMEDP
Dr. Ronald Steigerwalt, Pharmacology Team Leader, DMEDP
Dr. Gemma Kuijpers, Pharmacology Reviewer, DMEDP
Dr. Duu-Gong Wu, Chemistry Team Leader, DNDCII
Dr. Martin Haber, Chemistry Reviewer, DNDCII
Dr. Todd Sahlroot, Team Leader, Division of Biostatistics
Dr. Robert Shore, Reviewer, OCPB
Dr. Ronald Kavanagh, Reviewer, OCPB
Mr. Randy Hedin, PM, DMEDP

External participant Attendees and titles:

None

Meeting Objectives:

To determine if NDA [redacted] will be filed, and discuss plans for the review of the NDA.

Discussion Points:

Pharmacology: The application is fileable.

Biostatistics: The design of the study does not allow meaningful statistical inference. Therefore, the application does not require a statistical review.

OCPB: The application is not fileable; See attached filing review.

Clinical: The application is not fileable. See attached filing review.

Chemistry: The application is fileable.

Decisions (agreements) reached:

- The application is not fileable.

Unresolved or issues requiring further discussion:

- None

Action Items:

- Project manager will draft refuse to file letter.

Signature, minutes preparer: /S/

Concurrence Chair: /S/

cc: NDA Arch
HFD-510
Attendees
HFD-510/EGalliers/HAhn
HFD-511/RHedin/3.22.99/N21027.MN1
Concurrences: RKavanagh/RSteigerwalt/LLutwak/RShore/TSahlroot/3.22/
SSobel/GTroencle/GKuijpersDWu/MHaber/3.29.99

APPEARS THIS WAY
ON ORIGINAL

FILING COMMENTS - CLINICAL ASPECTS
DATE of MEETING: March 17, 1999

NDA No. 21-027
DRUG: HECTOROL, IV [1-alpha-OH vitamin D_2; doxercalciferol injection]
SPONSOR: Bone Care International
INDICATION: Management of secondary hyperparathyroidism

DATE SUBMITTED: Jan. 31, 1999
DATE RECEIVED: Feb. 2, 1999
MEDICAL REVIEWER: Leo Lutwak, M.D., Ph.D.

I. Background

Hectorol, in form of soft gelatin capsules containing a solution of drug in fractionated coconut oil, is under review for the same indications. The drug substance, 1-alpha OH vitamin D_2, is activated by the liver to 1,25- and 1,24- dihydroxy vitamin D_2, the biologically active substances. The Sponsor claims that the effect on secondary hyperparathyroidism of these substances is essentially similar to, but less toxic than, 1,25-dihydroxy vitamin D_3 (calcitriol), approved for this indication. The claim is made that the intravenous preparation shows "significant efficacy responses of 92.5% and 100.0% in treated patients participating in well-controlled clinical trials."

II. Material Submitted:

A. Paper: 14 volumes
B. Electronic: 2 **zip** drive disks

III. Studies Submitted

A. This NDA relies primarily on the studies submitted to NDA # 20-862 and IND # for the use of Hectorol in an oral dosage form.
B. A single study, Protocol No. H-114, using the intravenous preparation, is submitted. This was conducted at two multi-center sites, Los Angeles and Memphis, in the same population studied with the oral preparation in Protocol No. H-108. Initially, this was planned as a cross-over extension, with the subjects in the original study re-enrolled in an open-label regimen using the injectable material. Because the injectable formulation was not available for 6 months, the patients received oral or intravenous 1-alpha, 25-OH vitamin D_3 while awaiting enrollment.

IV. End-points

A. Efficacy: The sole efficacy endpoint was change in plasma PTH levels, expressed as: a) absolute values; b) % of initial (after "washout" phase) levels; c) time to achievement of specified % suppression.

B. Safety: Safety endpoints were the usual hematology and blood chemistry parameters, and specifically, development of hypercalcemia.

III. Problems with Submission:

A. Validity of claims is dependent on approval/non-approval of NDA No. 20-862 for the oral formulation of Hectorol. Many problems have been found in the studies submitted to this previous NDA.

B. The only studies bridging the oral and intravenous formulations are:

1. A small Phase I study of bioavailability
2. Historical data in the pivotal study H-114 relating results to the same patients when enrolled in study H-108. Although the present study was preceded by a "washout" phase, carry-over effects from the interim treatment cannot be ruled out.
3. None of the PK-PD studies of either the oral or intravenous preparations measured actual drug substance; all used measurements of 1,25-dihydroxy vitamin D.

IV. Recommendation: I am uncomfortable with recommending filing at this time.

A.

B.

Leo Lutwak, M.D., Ph.D.
Medical Officer
March 16, 1999

APPEARS THIS WAY
ON ORIGINAL

NDA 21-027
Hectorol IV
Bone Care International

Date:
March 29, 2000

CONTACT:
Ms. Darlene Kyllo
608-236-2530

MEMORANDUM OF TELECON

I telephoned Ms. Darlene Kyllo to discuss the Hectorol IV package insert. I told her the Division is requesting the following changes to the label:

1. In the **DESCRIPTION** section disodium edetate should be changed to disodium edetate 1.1.

2. In the **Clinical Studies** section change the number of patients evalutated to an intent-to-treat population (70), instead of

3. Take the following sentence out or the **DOSAGE AND ADMINISTRATION** section,

I further stated that these are preliminary comments and additional labeling requests may be made

/S/

Randy Hedin, PM

Note: The above recommendations were made at the request of the bone metabolism team leader.

APPEARS THIS WAY
ON ORIGINAL

cc: NDA Arch
HFD-510/EColman/MHaber/DWu
HFD-511/RHedin/3.29.00/N21027

NDA 21-027

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

Dear Ms. Kyllo:

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.

Also, refer to our fax dated on February 14, 2000.

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

1. Please provide your interpretation of the Pearson Correlation Coefficients provided in Table 1 in response to previous question # 13. Specifically, we are interested in your thoughts regarding the significant direct correlation between dose of Hectorol and PTH in H-114, but not in H-108.

2. Please provide your interpretation of the finding that the median weekly doses of Hectorol in H-108 decreased over the course of the 12 weeks of open-label treatment, whereas the median weekly doses in H-114 did not decrease during the corresponding time period.

3. For the 70 subjects (28 from LA and 42 from Memphis) who participated in both H-108 and H-114, please plot the mean weekly PTH values (observed data, not LOCF) along with the corresponding mean weekly Hectorol doses. Please plot the data for the 12-week open-label portions of H-108 and H-114 separately. If possible, plot these data in the same figure and submit on a diskette.

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