CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-027

MICROBIOLOGY REVIEW(S)

REVIEW FOR HFD-510
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF
MICROBIOLOGIST'S REVIEW #2 OF NDA

March 30, 2000

A. 1. NDA 21-027

SPONSOR Bone Care International
One Science Court
Madison, WI 53711

2. PRODUCT NAMES: Hectorol (doxercalciferol)

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: 2 µg/mL, ampule, IV

4. METHOD(S) OF STERILIZATION: [redacted]

5. PHARMACOLOGICAL CATEGORY: Vitamin D Hormone

6. DRUG PRIORITY CLASSIFICATION: S

B. 1. DATE OF INITIAL SUBMISSION: January 31, 1999

2. DATE OF AMENDMENT: February 17, 2000

3. RELATED DOCUMENTS: NDA 21-027

4. ASSIGNED FOR REVIEW: March 27, 2000

C. REMARKS: This submission was in response to microbiology deficiencies in the original submission.

D. CONCLUSIONS: This submission is recommended for approval on the basis of product quality microbiology.

Bryan Riley, Ph.D.

cc:

HFD 510/Consult File
HFD 510/R. Hedin
HFD 510/M. Haber
HFD 805/Consult File
HFD 805/B. Riley

Drafted by: B. Riley, 3/30/00
R/D initialed by: P. Cooney,

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ON ORIGINAL

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JAN 19 1999

REVIEW FOR HFD-510
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF
MICROBIOLOGIST'S REVIEW #1 OF NDA

January 14, 2000

A. 1. NDA 21-027

SPONSOR Bone Care International
One Science Court
Madison, WI 53711

2. PRODUCT NAMES: Hectorol IV (1-alpha-hydroxyvitamin D_2)

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: 1&2 mL ampules, 2µg/mL, Intravenous

4. METHOD(S) OF STERILIZATION: [redacted]

5. PHARMACOLOGICAL CATEGORY: Vitamin D Hormone

6. DRUG PRIORITY CLASSIFICATION: S

B. 1. DATE OF INITIAL SUBMISSION: January 31, 1999

2. DATE OF AMENDMENT: NA

3. RELATED DOCUMENTS:

4. ASSIGNED FOR REVIEW: November 17, 1999

C. REMARKS: The drug product is manufactured by [redacted]

APPEARS THIS WAY
ON ORIGINAL

D. CONCLUSIONS: This submission is approvable, pending resolution of microbiological deficiencies.

/S/ 1-14-00

Bryan Riley, Ph.D.

/S/ 1/19/00

cc:

HFD 510/Consult File
HFD 510/R. Hedin
HFD 510/M. Haber
HFD 805/Consult File
HFD 805/B. Riley

Drafted by: B. Riley, 1/14/00
R/D initialed by: P. Cooney,

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-027

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

FINAL

45 DAY FILING MEMO
OFFICE OF CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS

TO:	Randy Hedin, RPh, CSO HFD-510
FROM:	Ronald Evan Kavanagh, B.S. Pharm., Pharm.D., Ph.D.
THROUGH:	Hae Young Ahn, Ph.D., Team Leader
DATE:	16 March, 1999
NDA #	21-027
SUBMISSION DATE:	31 January 1999
BRAND NAME:	Hectorol®, 2.0 mcg/ml, 1 and 2 ml Ampules for Injection
GENERIC NAME:	Doxercalciferol
SPONSOR:	Bone Care International Madison, WI

SYNOPSIS:

Bone Care International has submitted NDA 21-027 for doxercalciferol injection (1α-hydroxy-vitamin D_2; Hectorol®) for 'the management of secondary hyperparathyroidism, [redacted] in patients undergoing chronic renal dialysis...'.

Doxercalciferol is a prodrug that is activated by hepatic CYP27 to 1,25-dihydroxy-vitamin D_2.

The pharmacokinetics of 5 mcg IV doxercalciferol was examined in protocol H-103. This study was included in NDA 20-862 for Hectorol Soft Gelatin Capsules. Study H-103 was conducted in elderly postmenopausal women with a different formulation than the to be marketed formulation. The protocol did not specify the rate of administration, used an assay that was determined to be invalid during the review of NDA 20-862, and did not examine doses used in the phase III efficacy study. Consequently this study is unacceptable for the current NDA.

(REF: 21 CFR 320.29 Analytical Methods for an in vivo Bioavailability Study)

RECOMMENDATION:

Based upon the presented information, the Office of Clinical Pharmacology and Biopharmaceutics finds that Hectorol® for Injection (doxercalciferol) NDA 21-027 is not filable.

COMMENTS TO THE MEDICAL OFFICER:

The dosing regimen of IV doxercalciferol used in the pivotal efficacy study (protocol H-114), is based on the 40% bioavailability observed in study H-103. Protocol H-103 was a crossover bioavailability study in elderly postmenopausal women, that compared 5 x 1 mcg of a SGC to 5 mcg (0.5 ml x 10 mcg/ml) of an IV formulation in an ethanol solution, (i.e. 5 mcg po to 5 mcg IV). Since gastrointestinal absorption decreases as dose increases it's likely that the conversion of the 10 mcg po dose to a 4 mcg IV dose will likely result in overdose. Additional comparative bioavailability studies are needed over the range of clinically used doses to obtain adequate information to support dosing of the IV formulation.

Pharmacokinetic studies of the IV formulation in ESRD and in the presence of hepatic disease are also necessary since, the effects of these disease states could be different with the IV formulation. Specifically elimination without alterations in absorption could be present in hepatic disease. In renal disease the shorter Tmax's and higher Cmax's superimposed on volume contraction due to dialysis could result significantly higher concentrations with the IV formulation than with the oral formulation. Consequently in both disease states could be significantly higher even accounting for differences in the amount absorbed.

COMMENTS TO BE SENT TO SPONSOR

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

A valid assay for pharmacokinetic studies is not available and needs to be developed (21 CFR 320.29). Comparative bioavailability of the IV and the to be marketed oral formulation over the entire range of clinically used doses needs to be established.

Ronald Evan Kavanagh, B.S. Pharm., Pharm.D., Ph.D.
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

RD initialed by Hae-Young Ahn, Ph.D., Team Leader_____

FT initialed by Hae-Young Ahn, Ph.D., Team Leader_____

CC: NDA #( ) (orig.,1 copy), HFD-510(Hedin, Lutwak, Troendel, Haber, Kuijpers), HFD-870(Shore, Ahn, M. Chen), CDR (Barbara Murphy).

Code: RF

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ON ORIGINAL

MAR 1 - 2000

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

NDA 21-027 / N-000	**SUBMISSION DATE:**	**31-JAN-99, 20-DEC-99, 22-FEB-00**
BRAND NAME:	**Hectorol**	
GENERIC NAME:	**Doxercalciferol 2.0 mcg/mL injection**	
REVIEWER:	**Robert M. Shore, Pharm.D.**	
SPONSOR:	**Bone Care International, Inc., Madison, WI**	
TYPE OF SUBMISSION:	**Original Application**	

TERMS AND ABBREVIATIONS:

AUCa-b ..... Area under the plasma-concentration-time curve from time a to time b
Cmax... ..... Maximum concentration
DMEDP ..... Division of Metabolic and Endocrine Drug Products
IM .... Intramuscular
ITT .... Intent to treat
OCPB .. .. Office of Clinical Pharmacology and Biopharmaceutics
PD .... Pharmacodynamic
PK .... Pharmacokinetic
PTH .... Parathyroid hormone
SC .... Subcutaneous
T½ .... Half-life
Tmax... ..... Time to maximum concentration

SYNOPSIS:

NDA 21-027/N-000 ('the IV NDA') is an original submission for Hectorol (doxercalciferol) injection for IV use in secondary hyperparathyroidism in renal dialysis patients. No new pharmacokinetic data have been submitted under this NDA. All pharmacokinetic data are cross-referenced to NDA 20-862/N-000 ('the oral NDA') for Hectorol 2.5mcg oral soft gelatin capsules approved 09-JUN-99. The initial oral dose is 10mcg three times a week.

NDA 21-027/N-000 relies only on cross-referencing the oral NDA for all the Section 6 (Human PK) data, which Dr. Kavanagh had found to be 'unacceptable' after a full review (dated 05-MAY-99) of NDA 20-862/N-000. The Agency decided it would 'Refuse to File' NDA 21-027/N-000 due to clinical factors. However, NDA 21-027/N-000 was 'Filed over Protest'.

The 31-JAN-99 submission contains no new Section 6 data and thus the same conclusion (i.e., 'unacceptable') that Dr. Kavanagh reached on the oral NDA should apply to the IV NDA. The submission on 20-DEC-99 includes a new pharmacodynamic analysis using PTH to compare the IV and PO Hectorol treatments. With this PD analysis, the sponsor attempts to establish therapeutic equivalence of the two therapies. However, the analysis is not appropriate for 'equivalence' because it is not a confidence interval approach and therapy is titrated to PTH response. It uses only mean differences in PTH measures to test differences at weekly intervals and, although the treatments tend not to be different, OCPB relies on a confidence interval approach to evaluate equivalence.

RECOMMENDATION:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation 2 (OCPB/DPE-2) has reviewed NDA 21-027/N-000 submitted 31-JAN-99 and 20-DEC-99. The overall Human Pharmacokinetic Section is not acceptable to OCPB because all pharmacokinetic data for this NDA is cross-referenced to NDA 20-862/N-000 which was deemed 'unacceptable'. The assay validation remains inadequate and the relative bioavailability of the oral dosage form was determined with not to-be-marketed formulations of both the oral and IV preparations. However, OCPB is aware that Hectorol is titrated to PTH response and has discussed the impact of the dubious pharmacokinetic data with DMEDP. As such, if Hectorol IV is approved, the recommended labeling changes should be made.

This recommendation and labeling comments (p. 6) should be sent to the sponsor as appropriate.

Table of Contents **Page**

(Appendices and/or Attachments available from DMEDP filing room or DFS, if not included)

BACKGROUND:

Vitamin D analogs help maintain calcium homeostasis in the body and are activated by hydroxylation. The kidneys and liver hydroxylate the 1 and 25 positions respectively to create the active 1-alpha-25-dihydroxy-vitamin D (1,25-OH-D) which helps to increase calcium absorption from the gut. In renal disease, the 1 position does not get hydroxylated resulting in diminished calcium absorption. In response the parathyroid gland produces PTH which, among other functions, promotes calcium resorption from bone to correct the lowered calcium levels. Since this can lead to renal osteodystrophy providing renal patients with exogenous vitamin D which does not need 1 hydroxylation may be a useful therapy.

Hectorol (doxercalciferol) is 1-alpha-hydroxy-vitamin D_2 (1-a-OH-D_2), a prodrug. Since it is already hydroxylated in the 1 position, renal patients may benefit from its administration as long as their liver can hydroxylate the 25 position and therefore activate it.

Currently, Hectorol 2.5 mcg soft gelatin capsule is approved at an initial dose of 10mcg orally three times a week. This dose is titrated based on PTH response with a target of 150 to 300pg/mL. The sponsor has submitted the current NDA in support of an intravenous formulation of Hectorol to be administered as a 4mcg dose three times a week with titration based on PTH.

DRUG FORMULATION:

Has the to-be-marketed formulation been used in the clinical trials?

The to-be-marketed formulation of Hectorol is listed below:

Statement of Ampule Composition

Component	Weight per Ampule (2 mL)	
	Absolute (mg)	Relative (%)
1α-OH-D_2	4.0 x 10-3	0.0002
TWEEN® Polysorbate 20, NF	8.0	0.40
Sodium Chloride, USP	3.0	0.15
Sodium Ascorbate, USP	20.0	0.99
Sodium Phosphate, Dibasic, USP,	15.2	0.75
Sodium Phosphate, Monobasic, USP,	3.6	0.18
Edetate, Disodium, USP	2.2	0.11
TOTAL		

It is to be supplied in 1 and 2mL glass ampules which are proportional in their composition. It has been used in the clinical trial submitted in the NDA.

Study H-103, the only study assessing IV pharmacokinetics of Hectorol, used an IV formulation (actual composition not available in current NDA).

ANALYTICAL METHODOLOGY:

Are the analytical methods acceptable?

No assay is available for the drug substance 1-a-OH-D_2. The for the active metabolite 1-25-OH-D_2 used in Study H-103 was unacceptable to Dr. Kavanagh reviewed under the oral NDA. No new data have been submitted, thus the same conclusion stands for the IV NDA.

HUMAN PHARMACOKINETICS AND BIOAVAILABILITY STUDIES:

I. Pharmacokinetics

What are the pharmacokinetic parameters of the IV formulation?

Study H-103, the only IV versus PO bioavailability study in the oral NDA, used a **not-TBM** IV formulation and a **not-TBM** oral capsule formulation. This study was conducted in post-menopausal osteopenic women aged 58-78 years. According to the oral NDA review this study demonstrated that the oral formulation had a [mean, CV] relative bioavailability of [41%, 44%] versus the IV formulation. This is probably the basis for a starting dose of 4mcg in the IV clinical trials.

The table below summarizes the pharmacokinetic information for Hectorol IV from Study H-103:

Parameter	Mean ± SD; CV
AUC0-48 (pg.hr/mL)[1]	1526 ± 758; 50%
AUC0-inf (pg.hr/mL)[1]	7056 ± 17218; 244%[2]
Cmax (pg/mL)[1]	51.06 ± 31.45; 62%
Tmax (hr)	8.00 ± 5.89; 74%

1 - Corrected for baseline concentration

2 - Subject No. 12 had T½ > 10 fold that of any other subject.

The elimination T½ for the IV formulation of Hectorol could not be determined.

Reviewer comments:
*Because the pharmacokinetic data from this study were generated with **not**-TBM formulations and the analytical methods were not adequately validated, labeling for the IV product should not emphasize results from study H-103. In contrast, although the same assay validation question applies, the oral labeling is the result of more studies and studies that were done with the TBM formulation.*

II. Pharmacokinetic / Pharmacodynamic Relationships

Has therapeutic equivalence between IV and PO Hectorol been established?

The 20-DEC-99 submission contains pharmacokinetic and pharmacodynamic data from NDA 21-027/N-000. The pharmacokinetic analysis is the same one included in NDA 20-862/N-000 which indicated that the bioavailability from the oral capsule is about 40% as compared to the IV formulation. However, any pharmacokinetic comparisons remain questionable since the validity of the analytical method remains in question.

Also in the 20-DEC-99 submission the sponsor has attempted to establish therapeutic equivalence using PTH levels from patients who received oral Hectorol and then were switched to IV Hectorol. There was an 8 week washout period before administration of each 12 week treatment. The plot below superimposes the mean 'percent of baseline' PTH response from each treatment during the 8 week washout and 12 week treatment periods. The sponsor has compared the mean weekly PTH levels in **the same patients** who received PO (Study H-108) and then IV (Study H-114) Hectorol. Two different patient population comparisons are included: All per-protocol subjects (N=64) who were switched from PO to IV and ITT subjects (N=70) who were switched from PO to IV. Below is a figure of the data for the all per-protocol subjects (the figure for the ITT subjects is similar):

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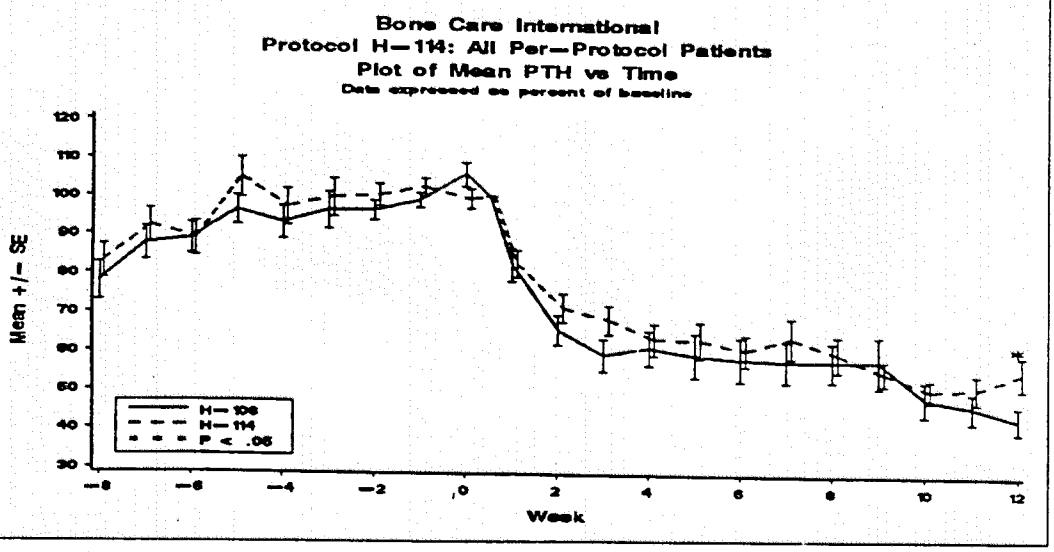
Comparative Pharmacodynamics (Per Protocol)

Hectorol Injection vs. Capsules



The figures indicate that the average 'percent of baseline' change is not statistically significantly different between the two treatments at weekly assessments. However, a more appropriate equivalence analysis would be a statistical analysis based on confidence intervals. That is, rather than looking at mean differences, calculate the AUC for PTH for each treatment in each patient (not 'percent of baseline' but actual PTH concentration), compute individual ratios (PTH_{IV}/PTH_{PO}), and calculate a 90% confidence interval about the mean ratio. The exact time point up to which the AUC should be calculated would have to be determined. The Medical Division could then evaluate the confidence interval and decide if it is acceptable to establish therapeutic equivalence. This would give a suggestion as to 'how comparable' the therapies are within subjects. In discussing this type of analysis with Dr Colman (DMEDP Medical Officer) it was thought this kind of equivalence analysis would add little to the NDA.

DISCUSSION:

Section 6 of the oral Hectorol NDA 20-862/N-000 was deemed unacceptable because of a number of issues. However, that review also indicted that labeling changes should be made if the NDA was to be approved. The pending Hectorol IV NDA 21-027/N-000 has cross-referenced the pharmacokinetic data from the oral NDA with no new information submitted. As such, the IV NDA is found to be unacceptable to OCPB but, if approved, labeling changes should be made.

COMMENTS FROM THE MEDICAL OFFICER:

1) Dr. Colman indicated that the pharmacodynamic equivalence analysis of PTH would not be necessary.

COMMENTS TO BE SENT TO MEDICAL OFFICER:

1) Under the Precautions section of the proposed labeling, the Geriatrics paragraph implies that 'geriatric' is age 70 years and over. According to a number of FDA Guidances, a geriatric patient is age 65 years

and over.

2) The 'Dosage and Administration' section does not indicate dosage adjustment when PTH is between 100 and 150 pg/mL.

3) It is suggested that an indication of the final titrated dose of IV Hectorol in the clinical studies be included in the 'Clinical Studies' section. This might give clinicians a general idea of dosage adjustments that would be expected.

LABELING COMMENTS:

The labeling included in the original 31-JAN-99 submission was not based on the approved labeling for oral Hectorol. This was because oral Hectorol had not yet been approved at the time when the IV Hectorol NDA was submitted. On 22-FEB-00 the sponsor submitted updated labeling based on the approved oral labeling. It is this updated labeling which is used as the basis for these labeling comments and is included in Appendix 1.

(~~Strikeout text~~ should be removed from labeling; Double underlined text should be added to labeling; ☞ indicates an explanation only and is not intended to be included in the labeling)

1) Under **'Pharmacokinetics and Metabolism'**
Peak blood levels of $1\alpha,25\text{-}(OH)_2D_2$ are reached at 8±5.9 hours (mean±sd) after a single intravenous ~~doses~~ of 5 µg of doxercalciferol. The mean elimination half-life of $1\alpha,25\text{-}(OH)_2D_2$ after an oral dose is approximately 32 to 37 hours with a range of up to 96 hours. The mean elimination half-life in patients with end stage renal disease (ESRD) and healthy volunteers appears to be similar after an oral dose. Hemodialysis causes a temporary increase in $1\alpha,25\text{-}(OH)_2D_2$ mean concentrations presumably due to volume contraction. $1\alpha,25\text{-}(OH)_2D_2$ is not removed from blood during hemodialysis.

☞ Editing for clarification.

Robert M. Shore, Pharm.D. /S/ 01-MAR-00
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

RD initialed by Hae-Young Ahn, Ph.D., Team Leader 24-FEB-00

CPB Briefing 01-MAR-00
attendees: HuangS, HuntJ, AhnH, JohnsonST, ShoreR.

FT initialed by Hae-Young Ahn, Ph.D., Team Leader /S/ 3/1/00

CC: NDA 21-027/N-000 (orig.,1 copy), HFD-510(Hedin), HFD-870(Ahn, HuangS), HFD-850(Lesko), CDR.

Code: AE

Appendix 1. Draft labeling (submitted 22-FEB-00)

6 Page(s) Redacted

Draft

Labeling

Note to File
OFFICE OF CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS

TO:	Randy Hedin, RPh, CSO HFD-510
FROM:	Ronald Evan Kavanagh, B.S. Pharm., Pharm.D., Ph.D.
THROUGH:	Hae Young Ahn, Ph.D., Team Leader
DATE:	July 27, 1999
NDA #	21-027
SUBMISSION DATE:	31 January 1999
BRAND NAME:	Hectorol®, 2.0 mcg/ml, 1 and 2 ml Ampules for Injection
GENERIC NAME:	Doxercalciferol
SPONSOR:	Bone Care International Madison, WI

Additional information regarding the assay was submitted by the sponsor on April 22, 1999 to the NDA for Hectorol® soft gelatin capsules (NDA 20-862).

The present NDA for Hectorol® for Injection references the NDA for the soft gelatin capsule for assay validation data. Consequently, assay information from the soft gelatin capsule NDA is pertinent to the present NDA for the injectable formulation.

A review of this additional information may be found in the file for the soft gelatin capsule formulation (NDA 20-862).

Recommendation:

Based upon the discrepancies between this submission and previous submissions to NDA 20-862, it is recommended that if Hectorol® for Injection is filed, a 'for cause' inspection is warrented to resolve these discrepancies.

/S/ 7/29/99

Ronald Evan Kavanagh, B.S. Pharm., Pharm.D., Ph.D.
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

RD initialed by Hae-Young Ahn, Ph.D., Team Leader 7/29/99

FT initialed by Hae-Young Ahn, Ph.D., Team Leader /S/

CC:NDA # 21-027 (orig.,1 copy)
HFD-510 (Hedin, Lutwak, Troendel, Haber, Kuijpers)
HFD-870(Shore, Ahn, M. Chen)
CDR (Barbara Murphy).

Code: NL