

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER: 020862**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

MAY 5 1999

**New Drug Application**  
**Clinical Pharmacology and Biopharmaceutics Review**

---

<b>NDA:</b>	20-862
<b>Generic Name:</b>	doxercalciferol
<b>Brand Name:</b>	Hectorol <sup>®</sup>
<b>Common Name:</b>	1-alpha-hydroxy-Vitamin D <sub>2</sub> (1 $\alpha$ -(OH)-D <sub>2</sub> )
<b>Sponsor:</b>	Bone Care International Madison, Wisconsin
<b>Submission Date:</b>	March 7, 1998 June 10, 1998 July 16, 1998 November 4, 1998 November 5, 1998 November 16, 1998 January 12, 1999 January 31, 1999
<b>Type of Submission:</b>	NME
<b>Reviewer</b>	Ronald Evan Kavanagh, B.S. Pharm., Pharm.D., Ph.D.
<b>Consultants:</b>	Robert Shore, Pharm.D. Carol Noory

---

**Synopsis****Background**

Vitamin D analogs are split (seco) sterols with antirachitic and hypercalcemic activity. Vitamin D<sub>2</sub> and D<sub>3</sub> are activated by 25 hydroxylation in the liver followed by hydroxylation in the kidneys at the 1 position to give the activated 1,25 dihydroxy Vitamin D's.

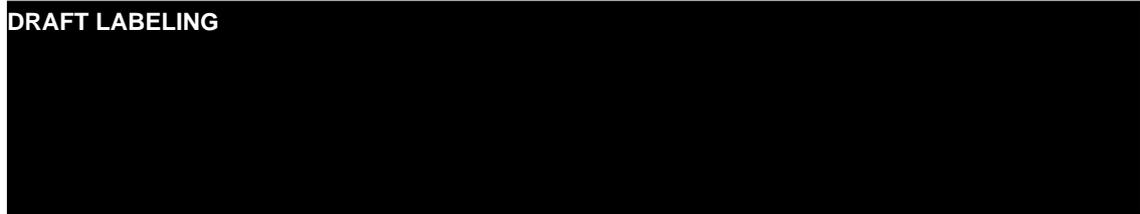
In renal failure 1 alpha hydroxylation does not occur and osteomalacia results, presumably as a consequence of secondary hyperparathyroidism. Thus in end stage renal disease (ESRD) administration of a form of vitamin D not requiring activation by the kidneys is necessary.

Hectorol<sup>®</sup> (doxercalciferol) is 1 $\alpha$ -hydroxy-Vitamin D<sub>2</sub> (1 $\alpha$ -(OH)-D<sub>2</sub>). Hectorol<sup>®</sup> requires activation by the liver, but not the kidneys, for biologic activity, resulting in the activated form 1 $\alpha$ ,25-dihydroxy-Vitamin D<sub>2</sub> (1 $\alpha$ ,25-(OH)<sub>2</sub>-D<sub>2</sub>).

There are 4 different types of vitamin D's currently on the market, and each are available from multiple sources.

**Proposed Indication and Dosage**

DRAFT LABELING


**Proposed Formulation**


**Major Issues**

- Assays have not been adequately validated.
- Food effects were claimed to be not present. This was based on a translation of a synopsis of a [REDACTED] study conducted with a tablet formulation, which is different from the to be marketed [REDACTED] formulation. Information on the fat content of the meal utilized in the study was not provided. [REDACTED]
- Drug interactions were not assessed, although based upon other Vitamin D's clinically significant drug interactions are expected to occur. An interaction with cholestyramine may have occurred in one trial.
- An adequate dissolution method has not been developed.
- Protein binding was not assessed with the active metabolite ( $1\alpha,25\text{-(OH)}_2\text{-D}_2$ ), it was only assessed with the inactive parent compound ( $1\alpha\text{-(OH)-D}_2$ ), which could not be measured in plasma or serum.
- Dose proportionality for the active metabolite does not appear to be present. The dose normalized oral bioavailability decreases upon going from 2 mcg to 5 mcg in a single dose study, with decreases also seen upon going from 5 to 15 mcg in a separate multiple dose study.
- Although the sponsor reports that hepatic disease has no effect on the pharmacokinetics of 1-alpha-hydroxyvitamin  $D_2$ , no firm conclusions can be drawn from this study due to
  - a) inadequate numbers of subjects
  - b) subjects with biliary disease were not identified and unequal blocking or absence of biliary disease could skew the results
  - c) a potential drug interaction with cholestyramine could have skewed the results.
- No statistical differences in pharmacokinetic metrics were shown between subjects with ESRD and normals. However based upon the exclusion of data, inadequate sampling, and the increase in concentrations post-dialysis, it appears likely that subjects with renal failure on hemodialysis have acute alterations in volume of distribution, increased half-life, and increased drug accumulation.
- The drug itself is highly toxic in pharmacologic doses and requires careful monitoring and titration to an effect on the surrogate marker PTH. However, titration to the desired therapeutic endpoint was rarely achieved in the clinical studies. Based upon the presented data there is insufficient data to provide adequate dosing guidelines for subjects with end stage renal disease (ESRD).

APPEARS THIS WAY ON ORIGINAL

**Recommendation**

The Office of Clinical Pharmacology and Biopharmaceutics / Division of Pharmaceutical Evaluation II has reviewed NDA 20-862 initially submitted March 7, 1998 (with additional submissions on June 10, 1998, July 16, 1998, November 4, 1998, November 5, 1998, November 16, 1998, January 12, 1999, and January 31, 1999) and finds it unacceptable.

If the NDA is not approved, the requested information under comments should be provided, if and when the NDA is resubmitted. However, if the NDA is to be approved the requested information is not imperative to have prior to approval and the information could be obtained post-approval. Capsule disintegration can be used on an interim basis. However the sponsor should develop a practical dissolution method and should submit a report to the FDA within one year of approval.

Please convey recommendations and comments to the sponsor as appropriate.

If the drug is approved labeling comments should be communicated to sponsor.

APPEARS THIS WAY ON ORIGINAL

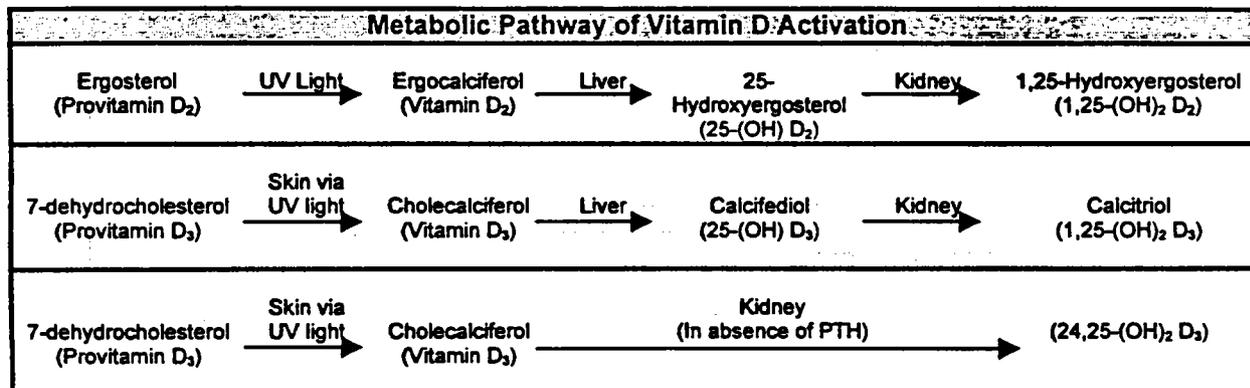
**Table of Contents**

<b><i>Topic</i></b>	<b><i>Page</i></b>
Background	5
Assay Methods and Validation	6
	6
	8
Bioavailability and Bioequivalence	11
<i>Absolute and Relative Bioavailability</i>	11
<i>Effect of Food</i>	13
Metabolism	13
<i>In vitro</i>	13
<i>In vivo</i>	13
Pharmacokinetics	13
<i>Normal Volunteers</i>	13
<i>Dose Proportionality</i>	16
<i>Patients</i>	19
<i>Protein Binding</i>	19
Special Populations	19
<i>Hepatic</i>	19
<i>Renal</i>	21
<i>Age</i>	23
<i>Gender</i>	23
<i>Pediatric</i>	23
<i>Race</i>	23
Drug Interactions	23
<i>In vitro</i>	23
<i>In vivo</i>	23
Pharmacokinetic/Pharmacodynamic Relationships	23
Dosage and Administration	24
Formulation	25
Dissolution	25
Reviewer Comments to Medical Officer	27
Comments to Firm	27
Labeling Comments	28
Signatures	28
Appendix I     Serum Concentration vs. Time Plots in Subjects with ESRD	29
Appendix II     Mean Parathyroid Hormone Concentrations vs. Time	32
Appendix III    PTH Concentrations Achieved with Dose Titration of Hectorol®	34
Appendix IV     Draft Labeling with Reviewer Comments	36

APPEARS THIS WAY ON ORIGINAL

I. Background

Vitamin D analogs are split (seco) sterols with antirachitic and hypercalcemic activity. Vitamin D<sub>2</sub> and D<sub>3</sub> are activated by 25 hydroxylation in the liver followed by hydroxylation in the 1 position by the kidneys.



In renal failure 1 alpha hydroxylation does not occur, and renal osteomalacia results; presumably as a consequence of secondary hyperparathyroidism. Thus administration of an activated form of vitamin D not requiring activation by the kidneys is necessary.

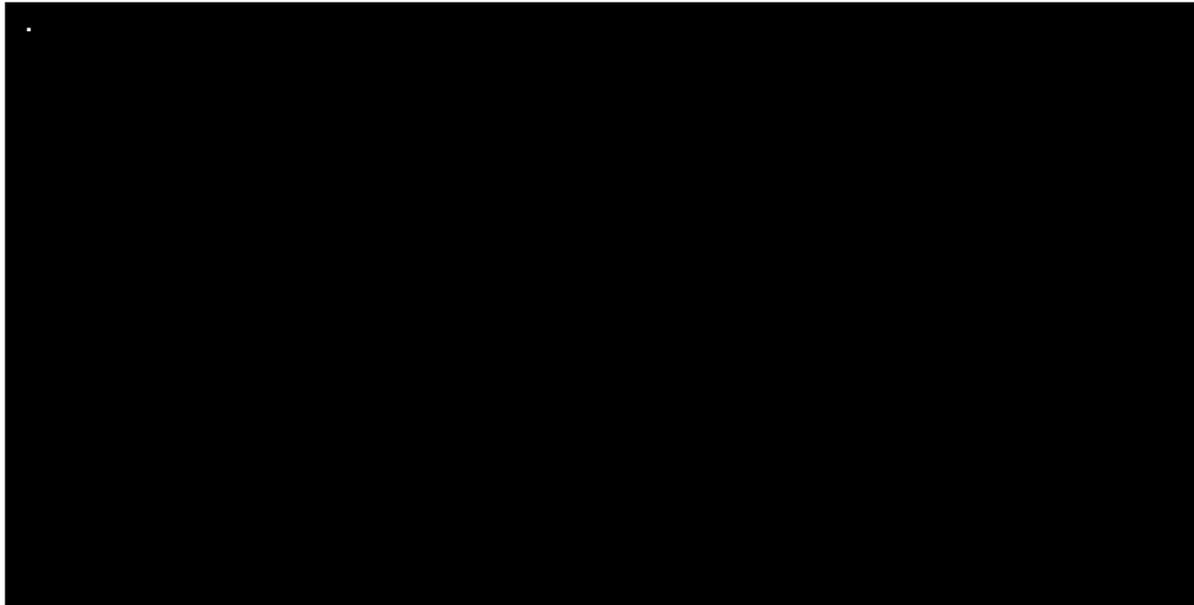
Hectorol® is 1α-hydroxy-Vitamin D<sub>2</sub> and only requires activation by the liver for biologic activity. Hepatic activation results in the activated form, 1α,25-dihydroxy-Vitamin D<sub>2</sub> (1,25-(OH)<sub>2</sub>-D<sub>2</sub>).

Currently available vitamin D's include

Currently Available Vitamin D's		
Vitamin D	Common Names	Selected Brands
Vitamin D <sub>2</sub>	Ergocalciferol	Drisdol® (Winthrop)
Vitamin D <sub>3</sub>	Cholecalciferol	Vitamin D <sub>3</sub> (Freeda; OTC)
25-(OH) Vitamin D <sub>3</sub>	Calcifediol	Calderol® (Organon)
1,25-(OH) <sub>2</sub> Vitamin D <sub>3</sub>	Calcitriol	Rocaltrol® (Roche)

APPEARS THIS WAY ON ORIGINAL

II. Assay Methods and Validation



**1,25-dihydroxyvitamin D<sub>2</sub>**

Parameter	Results
<i>Limit of Quantification</i>	
<i>Response Function</i>	
<i>Specificity</i>	

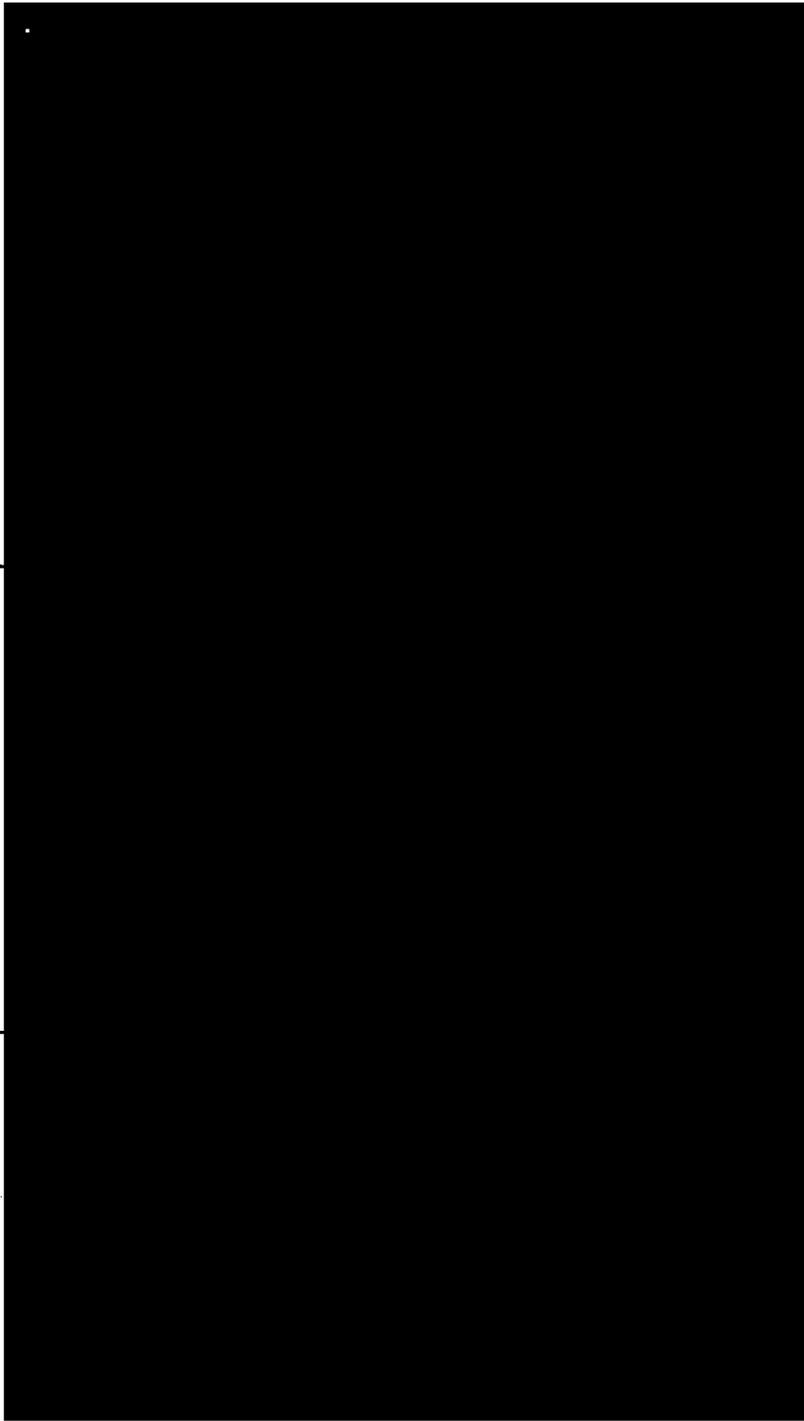
*Intra-assay accuracy*

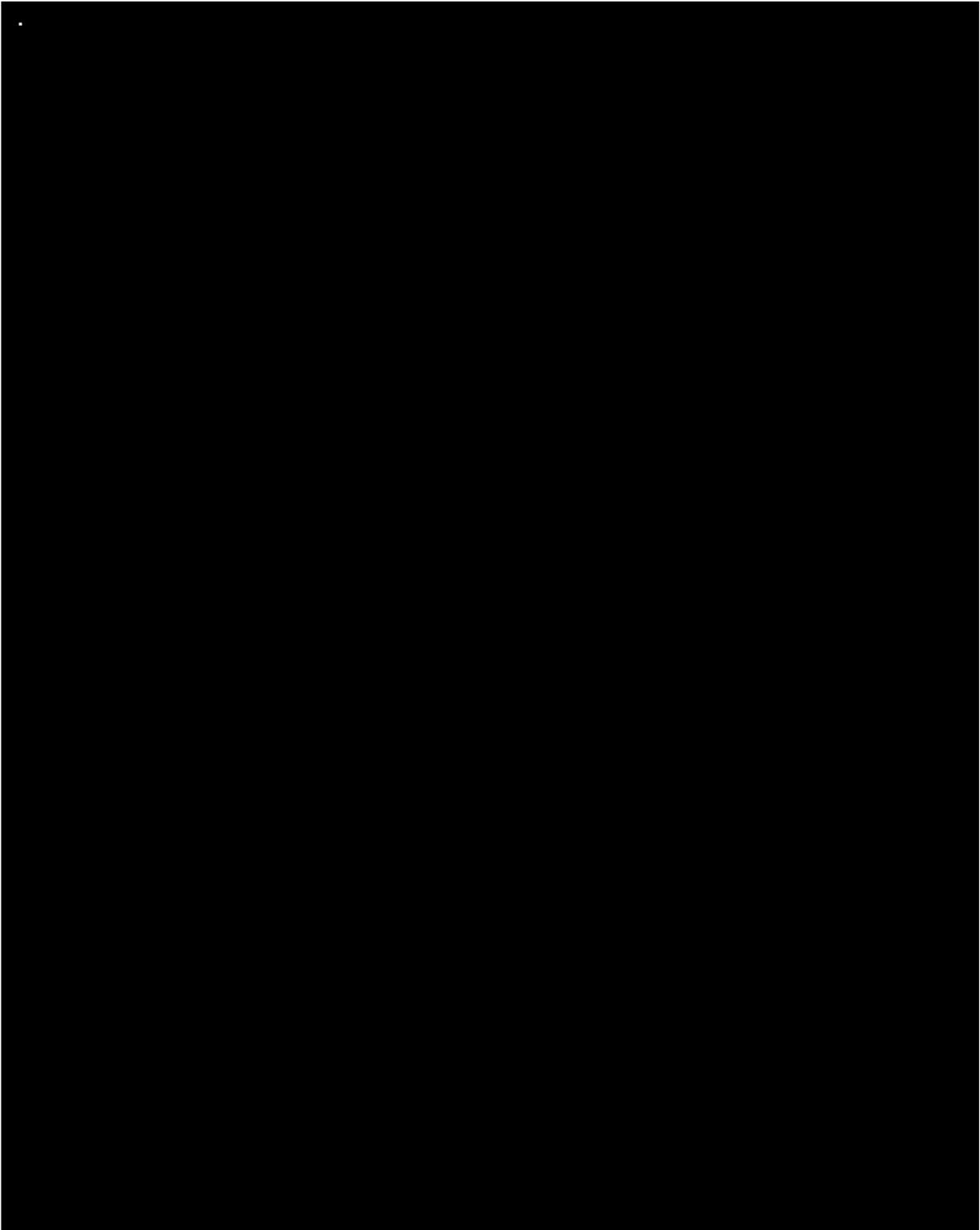
---

*Intra-assay precision*

---

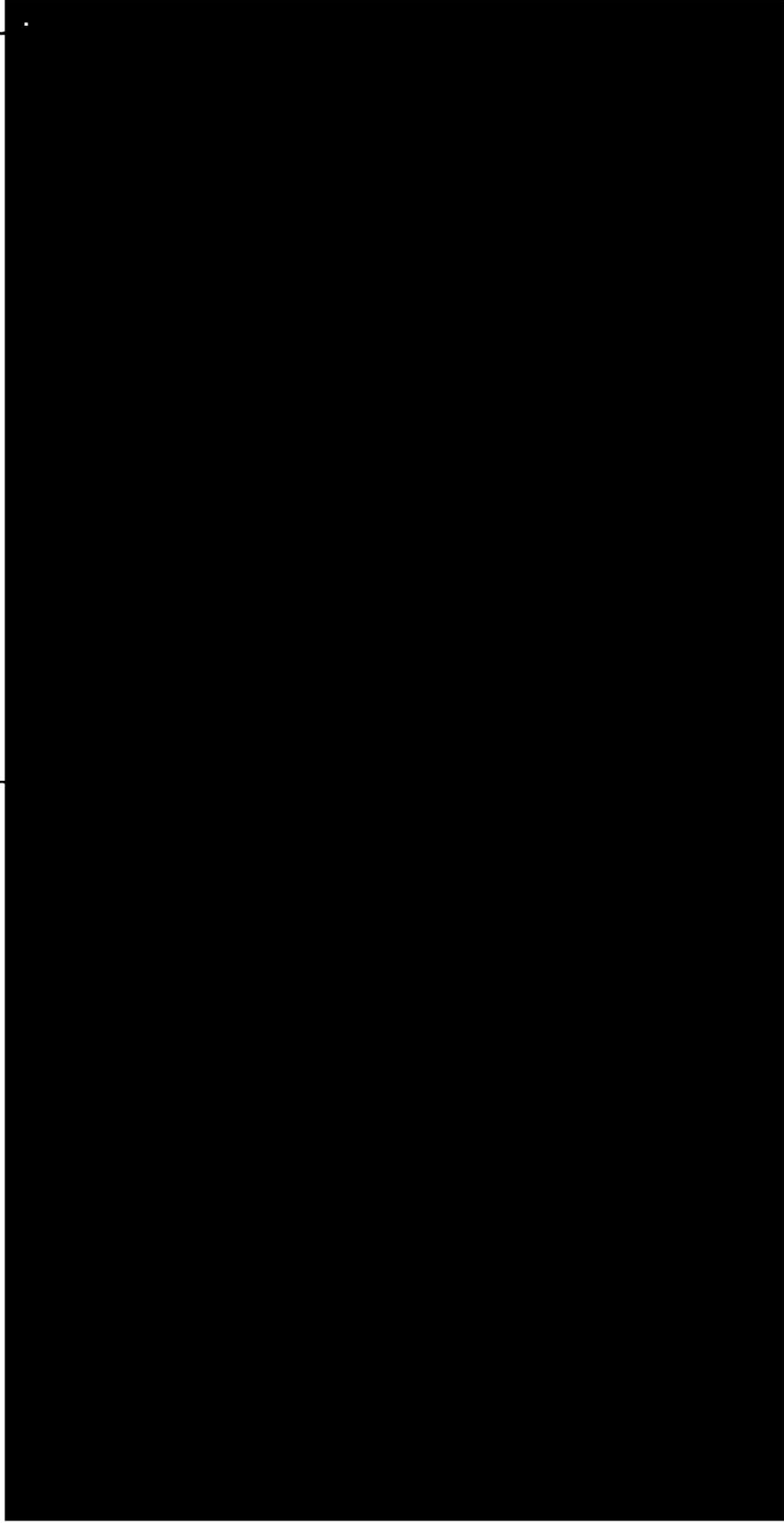
*Inter-assay accuracy*





*Intra-assay accuracy*

*Intra-assay precision*

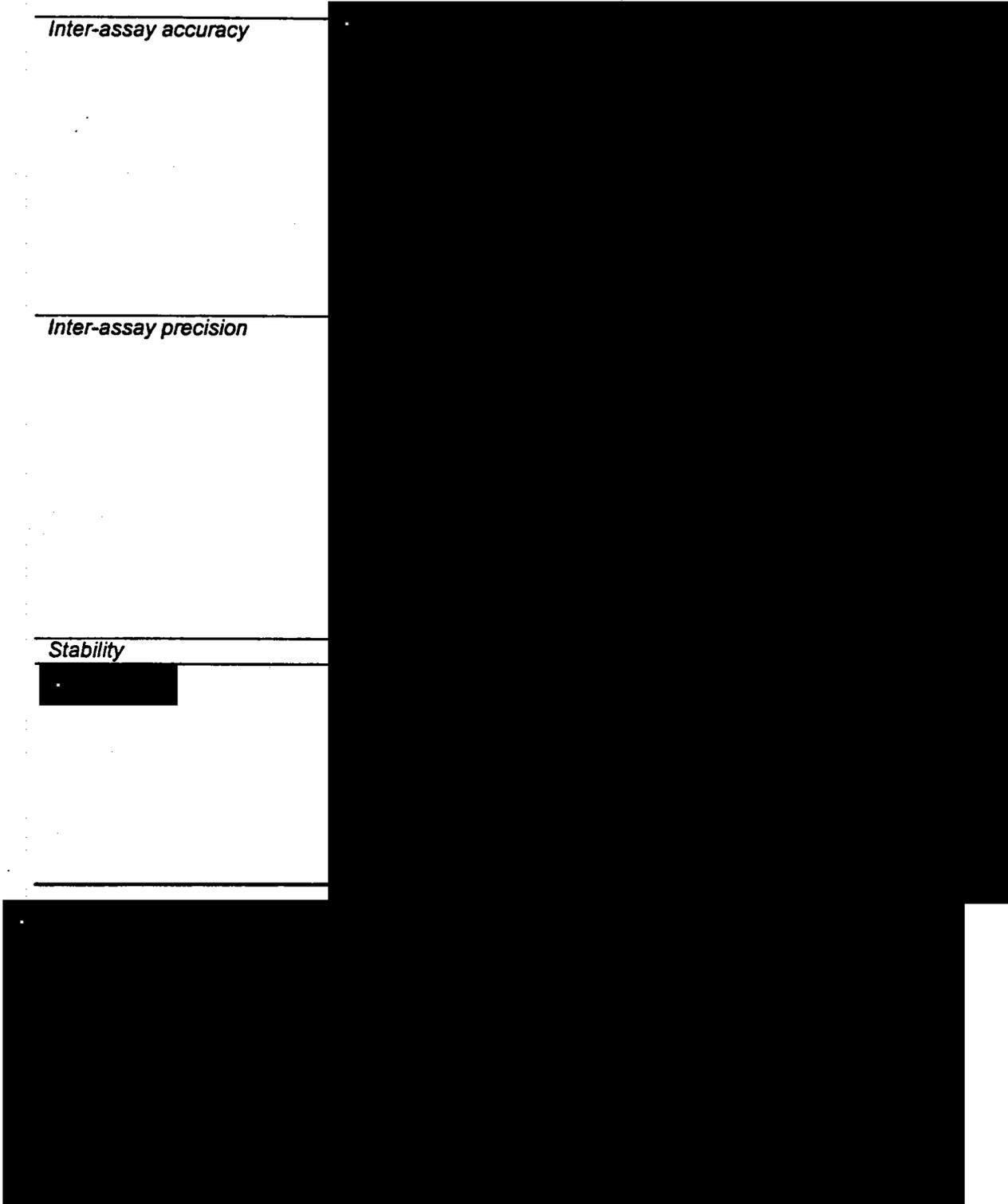


*Inter-assay accuracy*

*Inter-assay precision*

*Stability*

[Redacted]



### III. Bioavailability and Bioequivalence

Bioavailability and bioequivalence of the parent drug was not assessed due to assay limitations. Bioavailability is assessed indirectly through measurement of the active metabolite.

#### *Absolute and Relative Bioavailability*

This was an open label, randomized, single dose, 3 sequence, 3 treatment, 4 period (including a placebo run-in period) crossover study in 22 post-menopausal osteopenic women, aged from 58-78 yo.

Drug or placebo was administered in each period before breakfast as a total of 5 capsules (drug and/or placebo) in order to keep the dose of FCO constant. After administration subjects were confined to the clinic for 24 hours and meals during confinement were controlled for vitamin D content. Meals were identical in each of the 4 periods. The washout period between doses was 7 days. No mention is dosing is after an overnight fast, or the content of the breakfast.

Regimens were as follows:

- 5 x PBO SGC po (run-in period)
- 2 mcg po (2 x 1 mcg & 3 x PBO SGC po)
- 5 mcg po (5 x 1 mcg & 0 x PBO SGC po)
- 5 mcg IV (0.5 ml of 10 mcg/ml & 5 x PBO SGC po)

The sponsor claims that the mean absolute bioavailability for a single 5 mcg po dose is approximately 40% regardless of whether  $AUC_{0-48}$  or  $AUC_{0-\infty}$  is used for calculation. There are several points of interest regarding this study:

- Data is based [REDACTED]
- Subjects are post-menopausal women 58 – 76 yo with normal renal function and are thus not representative of the target population.
- $AUC_{0-\infty}$  is inaccurately estimated. This is secondary to the poor estimation of terminal half-life as the sampling was not long enough. Sampling was through 48 hours whereas the half-life is > 24 hours.
- This study was performed using a different formulation than the to be marketed formulation used in every other study. Consequently this data may not be extrapolable to the to be marketed formulation. Differences between formulations include the solvent for  $1\alpha$ -(OH)-Vitamin D<sub>2</sub> used prior to dilution, and the capsule size. The solvent was diethylether and the capsule strength was 1 mcg in the formulation used in the single dose bioavailability study (H103), whereas the solvent was ethanol and capsule strength was 2.5 mcg in all other studies.

APPEARS THIS WAY ON ORIGINAL

Study H103 - Single Dose 1 $\alpha$ -OH-D<sub>2</sub> Exposure using 1 mcg SGC Formulation of Hectoral®

Parameter	2 mcg PO Relative Exposure [2 mcg PO / 5 mcg PO] (F) <sup>1</sup>	2 mcg PO (2 x 1 mcg) Exposure relative to IV dose (F) <sup>1</sup>	5 mcg PO (5 x 1 mcg) Exposure relative to IV dose (F) <sup>1</sup>
AUC <sub>0-48</sub> (pg-hr/ml, per mcg dose)	1.39 ± 0.67 48.6	0.52 ± 0.28 53.45	0.41 ± 0.18 44.13
AUC <sub>0-∞</sub> (pg-hr/ml, per mcg dose) Including Data from Subject 012 <sup>2</sup>	2.38 ± 2.62 109.84	0.78 ± 0.98 126.34	0.43 ± 0.35 83.33
AUC <sub>0-∞</sub> (pg-hr/ml, per mcg dose) Excluding Data from Subject 012 <sup>2</sup>	2.40 ± 2.69 111.79	0.82 ± 0.99 121.17	0.45 ± 0.35 78.53

1 - Mean ± SD; CV; (Range)

2 - Subject No. 012 - t<sub>1/2</sub> > 10 fold greater than any other subject. AUC<sub>0-∞</sub> in subject 12 equaled 82,044 pg-hr/ml, i.e. > 16 fold greater than for any other subject

APPEARS THIS WAY ON ORIGINAL

### *Effect of Food*

According to a translated synopsis of a supportive food effect study performed in Japanese males receiving tablets, similar  $C_{max}$ 's and  $T_{max}$ 's were seen in both fed and unfed groups, whereas a higher AUC was seen in the fed group but this was 'not significantly different'.

There are two major caveats in accepting a conclusion of a lack of a food effect, including:

- a) A tablet formulation was used instead of the soft gelatin capsule formulation to be marketed in the United States.
- b) Details of the meal are not mentioned and it would be expected that a high fat meal might effect absorption of this fat-soluble vitamin. I expect that a fish and vegetable based diet would be typical in Japan and such meals would be low in fat as well as high in endogenous Vitamin D. Consequently, if a 'typical' Japanese meal was administered in this study, no food effect might be observed. However a food effect is expected with a high fat meal. Such high fat meals would be common in the US.

Consequently no conclusions can be drawn regarding the effect of a high fat meal on the bioavailability of the soft gelatin capsule formulation. Food effects are likely and need to be evaluated.

### **IV. Metabolism**

#### *In vitro*

Not assessed.

#### *In vivo*

Not assessed.

### **V. Pharmacokinetics**

#### *Normal Volunteers*

Pharmacokinetic parameters (i.e. clearance and volume of distribution) could not be estimated for either the parent compound or the active metabolite. However pharmacokinetic metrics (e.g.  $C_{max}$ ,  $T_{max}$ , AUC) of the active metabolite 1,25-Dihydroxy-Vitamin  $D_2$  were reported in both postmenopausal women with the 1 mcg SGC formulation after a single dose and in healthy male volunteers after multiple dosing with the to be marketed formulation. In both cases  $T_{max}$  occurred at approximately 11 hours post dose.

The half-life could not be accurately estimated in the single dose study (H103) as sampling was only to 48 hours, whereas it was apparent that the half-life in many subjects was greater than 24 hours. Thus half-life is not reported in this single dose study. A long half-life is supported by the fact that  $AUC_{0-48}$  is much less than 50% of  $AUC_{0-\infty}$ . However this also suggests that  $AUC_{0-\infty}$  is inaccurately estimated in this study.

APPEARS THIS WAY ON ORIGINAL

**Study H103 - Summary of Single Dose Pharmacokinetic Metrics in Postmenopausal Women**

Parameter	Placebo	2 mcg PO	5 mcg PO	5 mcg IV
AUC <sub>0-48</sub> (pg-hr/ml) <sup>1</sup>	205 ± 77	285 ± 146	540 ± 210	1526 ± 758
AUC <sub>0-∞</sub> (pg-hr/ml) <sup>1</sup>	Not Applicable	1107 ± 1902 <sup>2</sup>	1341 ± 1063	7056 ± 17218 <sup>3</sup>
C <sub>max</sub> (pg/ml) <sup>1</sup>	Not Applicable	9.99 ± 5.29 ██████████	17.38 ± 7.25 ██████████	51.06 ± 31.45 ██████████
Mean average baseline concentration <sup>4</sup> (pg/ml)	4.18 ██████████	Not Applicable	Not Applicable	Not Applicable
Mean average baseline concentration [AUC <sub>0-48</sub> / 48 hours] (pg/ml)	4.27 ± 1.61 ██████████	Not Applicable	Not Applicable	Not Applicable
T <sub>max</sub> (Hr)	Not Applicable	11.0 ± 4.4	11.1 ± 5.0	8.00 ± 5.89

1 – Corrected for baseline concentration

2 – Could not be estimated for 2 subjects

3 – Subject No. 012 – t<sub>1/2</sub> > 10 fold greater than any other subject based upon estimate of kel.

AUC<sub>0-∞</sub> in subject 12 equaled 82,044 pg-hr/ml, i.e. > 16 fold greater than for any other subject

4 – Mean across subjects of average concentration in each subject for all time points

5 – Half-life was not reported for this study

In contrast the mean terminal half-life was reported as 32 hours in the multiple dose study (H117) after 5 mcg (2 x 2.5 mcg) every other day (qod) and as approximately 37 hours after 15 mcg (6 x 2.5 mcg) qod, based upon sampling to 120 hours post-dose. Although the mean 37 hour estimate is an approximation, as some subjects had half-lives as high as 95 hours. Consequently their half-lives could not be accurately estimated.

Study H117 was an open label, randomized crossover design in normal 24 healthy volunteers (12 male & 12 female). Seventeen Caucasian and 7 African Americans participated, with treatment groups balanced for sex. The age range was 20-35 yo. Regimens were either 5 or 15 mcg (2 or 6 SGC) po qod x 5 doses (for 9 days) administered in the AM before breakfast. The meal given with the 5<sup>th</sup> dose was standardized as to content and quantity ('low in calcium and vitamin D') and the meals during the next 24 hours were controlled for vitamin D content. There was a minimum 2 week washout between regimens.

In addition to the caveats with the single dose study, the data does not include pharmacokinetic measures from a subject who dropped out due to hypercalcemia. This subject could conceivably be an outlier with respect to pharmacokinetic parameters.

In both studies mean T<sub>max</sub> was approximately 11 to 11.5 hours and was independent of dose and formulation.

**Study H117 - Summary of Multiple Dose Pharmacokinetic Metrics in Healthy Normal Volunteers with to be Marketed Formulation**

Parameter	5 mcg QOD	15 mcg QOD
	Mean $\pm$ SD CV (Range)	Mean $\pm$ SD CV (Range)
C <sub>max</sub> <sup>a</sup> (pg/ml)	29.90 $\pm$ 17.65 59.03 (7.87 - 74.52)	67.07 $\pm$ 36.33 54.16 (30.77 - 150.03)
C <sub>min</sub> <sup>a</sup> (pg/ml)	11.6 $\pm$ 9.0 <sup>b</sup> 83.16 (-1.03 - 41.17)	26.33 $\pm$ 17.14 65.12 (4.92 - 72.63)
Absolute Swing <sup>a</sup> (C <sub>max</sub> - C <sub>min</sub> )	18.85 $\pm$ 12.77 67.78 (5.00 - 47.1)	40.75 $\pm$ 22.97 56.37 (14.20 - 104.3)
AUC <sub>0-48</sub> <sup>a</sup> (Corrected for Baseline Concentration)	957 $\pm$ 533 56 (184 - 2118)	2168 $\pm$ 1119 52 (770 - 4953)
Terminal Half-Life	31.96 $\pm$ 11.01 34.45 (12.58 - 55.37)	37.01 $\pm$ 16.13 43.59 (21.36 - 95.41)
T <sub>max</sub> (hr)	11.6 $\pm$ 5.7 49.07 (4.08 - 24.03)	11.54 $\pm$ 5.5 47.60 (4.00 - 23.93)

- a All values are corrected for baseline  $1\alpha,25\text{-(OH)}_2\text{-Vitamin D}_2$  concentrations.  
b n=23 for C<sub>min</sub> for the normal subjects (value for Subject No. 024 in Study No. H-117 was negative after baseline subtraction and this value was excluded from calculation of mean and SD).  
c Data was not obtained from subject who dropped out due to hypercalcemia.

APPEARS THIS WAY ON ORIGINAL

*Dose Proportionality*

Dose proportionality is unlikely. It appears that bioavailability decreases upon going from 2 to 5 mcg po, and further decreases upon going from 5 to 15 mcg po and that dose disproportionality is independent of formulation.

In the single dose study (H103) the 90% confidence interval for the dose adjusted ratio of a 2 mcg po single dose to a 5 mcg po single dose, is greater than 1.0 at the lower limit and 1.49 or greater at the upper limit for both AUC and C<sub>max</sub>. This particular study used the initial 1 mcg formulation in post-menopausal women.

(See Table - Study H103- Dose Normalized Pharmacokinetic Metrics for 1,25-Dihydroxyvitamin D<sub>2</sub> - 1 mcg formulation)

The lack of dose proportionality also tends to hold with the to be marketed formulation upon going from 5 mcg po to 15 mcg po with qod multiple dosing. This is evidenced by the lower dose adjusted AUC and C<sub>max</sub> after 15 mcg po relative to 5 mcg po within subjects, as shown in the following table.

(See Table - Study H117 - Dose Adjusted Pharmacokinetic Metrics in Healthy Normal Volunteers - 2.5 mcg formulation)

APPEARS THIS WAY ON ORIGINAL

Study H103- Dose Normalized Pharmacokinetic Metrics for 1,25-Dihydroxyvitamin D<sub>2</sub> - 1 mcg formulation

Parameter	2 mcg PO	5 mcg PO	5 mcg IV	P-value for treatment effect	90% CI for ratio of doses (2 mcg PO / 5 mcg PO)
AUC <sub>0-48</sub> (pg-hr/ml, per mcg dose)	143 ± 73	108 ± 42	305 ± 152	0.0001 2 mcg PO < 5 mcg IV 5 mcg PO < 5 mcg IV	1.01 - 1.49
AUC <sub>0-∞</sub> (pg-hr/ml, per mcg dose)	554 ± 951	268 ± 213	661 ± 228	0.0001 2 mcg PO < 5 mcg IV 5 mcg PO < 5 mcg IV	1.04 - 2.11
C <sub>max</sub> (pg/ml, per mcg dose)	5.00 ± 2.65	3.48 ± 1.45	10.2 ± 6.3	0.0001 2 mcg PO < 5 mcg IV 5 mcg PO < 5 mcg IV 5 mcg PO < 2 mcg PO	1.14 - 1.65
T <sub>max</sub> (Hr)	11.0 ± 4.4	11.1 ± 5.0	8.00 ± 5.89	0.0751	Not Applicable

1 - Subject No. 012 excluded; un-normalized AUC<sub>0-∞</sub> in subject 012 was > 16 fold greater than for any other subject

APPEARS THIS WAY ON ORIGINAL

**Study H117 - Dose Adjusted Pharmacokinetic Metrics in Healthy Normal Volunteers - 2.5 mcg Formulation**

Parameter	5 mcg PO Dose every 48 hours	15 mcg PO Dose every 48 hours	Statistical P-Value for Treatment Effect	Intrasubject Ratio (15 mcg PO / 5 mcg PO) Mean ± SD CV (Range)	Schulmann's Two One-sided 90% Confidence Interval for Ratio of Doses (15 mcg PO / 5 mcg PO)
AUC <sub>0-48</sub> (pg-hr/ml, per mcg dose)	191 ± 107	145 ± 75	0.012	0.856 ± 0.335	0.69 - 0.92
C <sub>max</sub> (pg/ml, per mcg dose)	5.98 ± 3.53	4.47 ± 2.42	0.017	0.857 ± 0.354 41.31 (0.359 - 1.454)	0.67 - 0.92
C <sub>min</sub> (pg/ml, per mcg dose)	2.32 ± 1.80	1.76 ± 1.14	0.939	Not provided	0.68 - 1.4
C <sub>max</sub> - C <sub>min</sub> (pg/ml, per mcg dose)	3.77 ± 2.55	2.72 ± 1.53	0.013	0.839 ± 0.344 41.00 (0.308 - 1.469)	0.65 - 0.91
T <sub>max</sub> (hr)	11.6 ± 5.7	11.5 ± 5.5	0.973	Not provided	Not Applicable

n=23 for C<sub>min</sub> for the normal subjects as value for Subject No. 024 in Study No. H-117 was negative after baseline subtraction).

APPEARS THIS WAY ON ORIGINAL

*Patients*

See special population – renal failure.

*Protein Binding*

Protein binding was assessed in pooled plasma by ultracentrifugation for the parent drug 1 $\alpha$ -(OH)-D<sub>2</sub>. In addition to not assessing the active moiety, individual types of protein such as albumin and specific proteins known to bind and transport Vitamin D's were not assessed.

The reported value was  $92.3 \pm 1.3$  % (mean  $\pm$  SD) over the range 1 to 100 ng/ml (1000 to 100,000 pg/ml). These concentrations are approximately 2.42 to 242.3 nM/L whereas the albumin concentration is approximately 0.6 mM/L and the vitamin D specific binding protein concentration is approximately 5 – 8  $\mu$ M/L, consequently variations in protein binding are unlikely to occur.

**VI. Special Populations***Hepatic*

Nineteen subjects (twelve men and seven women) participated in an open-label repeated-dose pharmacokinetic study. The enrolled subjects were between 40 and 70 years of age, inclusive. Subjects in each cohort were age- and sex-matched to the extent possible. The subjects included the following subsets:

- four normal healthy subjects
- ten subjects with mild hepatic impairment (5-6 points\*)
- two subjects with moderate hepatic impairment (7-9 points\*)
- three subjects with severe hepatic impairment (10-15 points\*)

\* - point score determined by the Pugh modification of Child-Turcotte criteria for assessing hepatic impairment

Subjects were administered 1 $\alpha$ -OH-D<sub>2</sub> 10 mcg (4 x 2.5 mcg) po for 8 doses qod before breakfast. Predose blood samples were taken on days 9, 11, 13 and 15 and then up to 168 hours after the last dose.

APPEARS THIS WAY ON ORIGINAL

## Results:

Parameter	Mild Hepatic Disease (n=8)	Moderate Hepatic Disease (n=2) <sup>a</sup>	Severe Hepatic Disease (n=3)	Normal Subjects (n=4)	Statistical P value for a subject-group difference (and for a trend among subject groups)
AUC (pg-hr/ml)	682 ± 504	85 ± 87	738 ± 646	711 ± 502	0.067 (0.277)
C <sub>max</sub> (pg/ml) (Baseline Corrected)	20.5 ± 12.9	7.1 ± 0.4	21.0 ± 17.8	22.3 ± 14.7	0.417 (0.334)
C <sub>min</sub> (pg/ml) <sup>a</sup>	7.7 ± 7.1	0.0 ± 0.0	8.0 ± 9.6	6.4 ± 5.6	0.786 (0.762)
C <sub>max</sub> -C <sub>min</sub> (pg/ml)	13.2 ± 6.3	9.0 ± 2.3	13.2 ± 8.0	15.9 ± 10.0	0.846 (0.522)
t <sub>max</sub> (hr)	9.3 ± 3.0	12.0 ± 5.7	13.3 ± 9.5	11.8 ± 9.0	0.771 (0.631)
t <sub>1/2</sub> (hr) <sup>b,c</sup>	44.3 ± 26.6	b	35.8 ± 8.8	33.0 ± 27.0	

- a Both subjects with moderate hepatic disease (Nos. 201 and 202) and one subject from each of the other three groups had baseline-corrected trough concentrations of 0. All such subjects were omitted from the ANOVA, which required log transformation. Accordingly, the statistical P-value shown reflects calculations with these data missing, and a comparison between three groups only, i.e., excluding the group with moderate hepatic disease (Subject Nos. 201 and 202).
- b Half-life was not provided for subjects with moderate hepatic disease (Nos. 201 and 202). Statistical analysis was not performed for half-life for any group. Estimates of half-life are based upon last 3 or 4 concentrations that are at least double the baseline concentration (except in 1 subject where it's double the limit of detection). Mean half-life for normal subjects excludes half-life from subject no. 403.

No differences were found in pharmacokinetic parameters by statistical analysis, and graphs of mean plasma concentration vs. time charts, show mean data from different groups are virtually superimposable.

The sponsor claims that hepatic disease has no effect on the pharmacokinetics of 1-alpha-hydroxyvitamin D<sub>2</sub>, however no firm conclusions can be drawn from this study due to the following concerns:

- Absorption (and possibly elimination) might be effected by alterations in biliary secretion of bile acids and drug. The Pugh-Child scale is a composite scale and its' use does not mean that subjects with biliary impairment were included, or in sufficient number or severity to detect an effect. Neither is the data nor data analysis sufficient to determine if subtypes of liver disease could effect kinetics.
- Statistical analysis did not include subjects with moderate hepatic disease. Although even if they had been included, the significance of lower concentrations in these subjects is unknown due to the group having only two subjects. In addition estimation of pharmacokinetic metrics may not be reliable in these subjects due to assay insensitivity and low concentrations.
- The group with severe hepatic disease included only 3 subjects, and one subject (Subject 302) was receiving cholestyramine. Cholestyramine would be expected to inhibit absorption

of fat soluble vitamin D. This subject had very low concentrations of  $1,25\text{-(OH)}_2\text{-D}_2$  (Cmax of 4.1 pg/ml compared to 19.4 and 39.5 pg/ml in the other 2 subjects). Excluding the data from this subject increases the mean Cmax from 21.0 to 29.45 pg/ml. Similarly AUC in this subject was 131 pg/ml x hr<sup>-1</sup> compared to 665 and 1418 pg/ml x hr<sup>-1</sup> in the other two subjects. Excluding the data from this subject increases the mean AUC from 738 to 1041.5 pg/ml x hr<sup>-1</sup>. Consequently this single subject could have significantly biased the results.

- Several subjects had ascites and many were receiving multiple medications. Plasma protein production is usually abnormal in subjects with severe hepatic impairment. No attempts were made to determine if these factors could effect the results.
- Estimation of half-life is questionable. Estimation of half-life by visual inspection is significantly different from estimates of half-life presented in the study report. For example subject no. 403 was reported to have a half-life of 44.5 hours, yet concentrations are decreasing and visual inspection suggests a half-life of approximately 100 hours or greater (see attached). Estimates of half-life for other individuals also appear to be in error.

### Renal

Pharmacokinetics of  $1\alpha\text{-OH-D}_2$  in patients with ESRD was studied in an open label trial in 13 subjects 29–73 yo on hemodialysis 3 times per week. There was a 1 week washout for vitamin D analogues followed by  $1\alpha\text{-OH-D}_2$  10 mcg (4 x 2.5 mcg) po x 5 doses qod (days 1,3,5,7,9) followed by 5 mcg (2 x 2.5 mcg) po x 5 doses qod (days 11,13,15,17,19). The dialysate contained between 2 and 3.5 mEq of Ca<sup>++</sup>. After the last dose, an identical meal was served to all subjects at 30 minutes post-dose. Blood samples for  $1\alpha,25\text{-(OH)}_2\text{-D}_2$  were obtained before hemodialysis on day 8 and after hemodialysis on days 8, 15, 17. After the last dose of  $1\alpha\text{-OH-D}_2$  on day 19 a complete pharmacokinetic profile was obtained with sampling through 240 hours post-dose, with continuing hemodialysis 3 times per week.

Hemodialysis with its attendant fluid removal appears to acutely effect the volume of distribution, as concentrations consistently increased post-dialysis compared with pre-dialysis concentrations. For example:

Mean Day 8 Concentrations	
Pre-dialysis	post-dialysis
37.55 ± 11.97	54.13 ± 28.74

The sponsor claims that  $1\alpha,25\text{-(OH)}_2\text{-D}_2$  is not removed by dialysis, nor would we expect dialysis to eliminate  $1\alpha,25\text{-(OH)}_2\text{-D}_2$  as it is poorly water soluble, however this was not evaluated.

The sponsor's second conclusion was that pharmacokinetic metrics are similar in patients on hemodialysis and healthy normal subjects. However this conclusion is not based on reliable data, thus no firm conclusions can be reached.

Representative graphs of serum concentration time profiles from two subjects are provided in Appendix I. The graph from subject 11 is exceptionally smooth and demonstrates the low concentrations, the Tmax, and the biphasic elimination. The graph from subject 12 is not as smooth and is representative of many of the subjects. Intermittent increases in concentration at 72 and 168 may indicate the effect of hemodialysis and volume contraction. Alternatively the 96 hour and subsequent concentrations may simply reflect assay and baseline variability.

## Comparison of Pharmacokinetic Metrics in Subjects with ESRD Receiving 5 mcg po qod x 5 Doses

Parameter <sup>a</sup>	All ESRD Patients (n = 11) <sup>e,f</sup>	Those ESRD Patients with t <sub>1/2</sub> Allowing Steady State to be Reached (t <sub>1/2</sub> ≤ 58 hr) (n = 7) <sup>d,e,f</sup>	Normal Subjects (Data from Study H-117) (n = 24)	Statistical P-value for all ESRD Patients vs. Normals (& for ESRD patients with t <sub>1/2</sub> ≤ 58 hr vs. normals)
AUC (pg-hr/ml)	1232 ± 731	1165 ± 629	957 ± 533	0.254 (0.439)
C <sub>max</sub> (pg/ml)	38.0 ± 21.1	38.4 ± 21.4	29.9 ± 17.7	0.295 (0.395)
C <sub>min</sub> (pg/ml)	13.6 ± 10.0	11.4 ± 6.8	11.6 ± 9.0 <sup>p</sup>	0.375 (0.641)
C <sub>max</sub> - C <sub>min</sub> (pg/ml)	24.5 ± 13.6	27.0 ± 15.1	18.9 ± 12.8	0.322 (0.256)
t <sub>max</sub> (hr)	12.4 ± 2.8	12.0 ± 3.3	11.6 ± 5.7	0.662 (0.849)
t <sub>1/2</sub>	61.0 ± 42.2 ████████████████████	38.4 ± 12.0	31.96 ± 11.01	Not performed.
t <sub>1/2</sub> Excluding data from days on dialysis	45.8 ± 24.7 ████████████████████	36.3 ± 13.3	Not applicable	Not performed.

- a. Values are corrected for baseline 1α,25-(OH)<sub>2</sub>-Vitamin D<sub>2</sub> concentrations.
- b. n=23 for C<sub>min</sub> for the normal subjects (value for Subject No. 024 in Study No. H-117 was negative after baseline subtraction).
- c. One subject was reported to have a negative half-life, however there is a mistake in the calculations. The half-life is definitely positive as log concentrations are declining linearly. Consequently mean half-life is even longer.
- d. Some subjects received the 10 mcg loading dose regimen for greater than 5 doses. Thus it's unclear if some of these subjects may have received less than 5 doses and therefore may not have been at steady-state. Consequently steady-state metrics are suspect as the concentration may reflect the loading dose. Unfortunately data was not provided to allow separation out of these subjects.
- e. Thirteen of 16 subjects completed the renal dialysis study and 11 were evaluable for pharmacokinetic parameters, of these only 7 achieved steady state.
- f. Three subjects were discontinued early due to hypercalcemia. Unfortunately samples for Vitamin D concentrations were not obtained, thus concentrations and metrics in ESRD could run higher than reported.

Although there were no statistically significant differences in pharmacokinetic metrics from patients on dialysis and historical values from healthy normal subjects, firm conclusions can not be made. If sampling had been long enough, data had not been excluded from subjects who dropped out due to toxicity, and if steady state had been achieved, there may have been a difference observed between subjects with ESRD on hemodialysis and normal subjects. Including

possibly increases in half-life and evidence of increased drug accumulation.

#### Age

Not assessed, although women up to 76 years old were studied in the bioavailability study in osteoporotic women and subjects up to 75 years old were included in the phase II and III ESRD studies.

#### Gender

Not assessed, although both men and women were studied.

#### Pediatric

Not assessed.

#### Race

Not assessed, although African-Americans made up the vast majority of subjects in the phase II and III ESRD studies.

### VII. Drug Interactions

#### *In vitro*

Not performed

#### *In vivo*

Although *in vivo* drug interaction studies were not performed, the absorption and elimination of vitamin D analogs are expected to be dependent on bile acid secretion. Consequently any drugs that effect bile acid production or homeostasis would be expected to alter bioavailability, enterohepatic recycling, and elimination.

### VIII. Pharmacokinetic/Pharmacodynamic Relationships

Data to assess pharmacokinetic/pharmacodynamic relationships were provided in the clinical data section. Two phase II and two phase III studies were performed in subjects with end stage renal disease (ESRD).

In the first phase II study (H-106) drug was dosed at 4.0 mcg daily before breakfast. Dialysate calcium concentration was 2.5 mEq for all subjects and the concentration was adjusted downward for low intact parathyroid hormone concentrations (iPTH). For mild hyperphosphatemia or hypercalcemia the dose of phosphate binders could be adjusted.

There were no clear PK/PD relationships, however intact PTH concentrations showed a downward trend throughout the 12 weeks of the treatment phase and were continuing to decrease at the end of the study (See Appendix II). Thus the Consequently drug exposure and/or effect had not been stabilized. In addition a number of subjects had to be discontinued from the study early due to an excessive effect on iPTH or calcium or phosphate. Plus even at the end of 12 weeks the mean PTH concentration was not within the target range of 150 to 300 pg/ml. Thus it appears that 12 weeks is inadequate to address the issue of dosing.

In the second phase II study (H-110) drug was dosed at 10.0 mcg 3 times weekly following hemodialysis. Dialysate calcium concentration was 2.5 mEq for all subjects. Subjects were discontinued from the study for low PTH concentrations and dose was adjusted downward for

markedly elevated calcium or phosphate concentrations. There was no upward dose adjustment for persistently elevated intact parathyroid hormone concentrations (iPTH).

Of 10 subjects, 5 had to be discontinued due to excessively low PTH concentrations. Of the rest, only 1 of 5 had PTH concentrations within the proposed target range of 150 – 300 pg/ml; 1 was slightly outside this range at 149.1 pg/ml, and 3 had excessively high concentrations of 494.0, 973.6 and 1021.1 pg/ml at the end of the study. There was no clear relationship between Vitamin D concentrations and iPTH at the end of the study.

Two identical phase III studies were also performed. They differed only in their location and as a result the demographics of the patient population varied by site. However, African-Americans made up the majority of the subjects at both sites. In these studies dialysate concentration could be varied, in addition  $1\alpha$ -(OH)-Vitamin D<sub>2</sub> dose could be both increased and decreased.

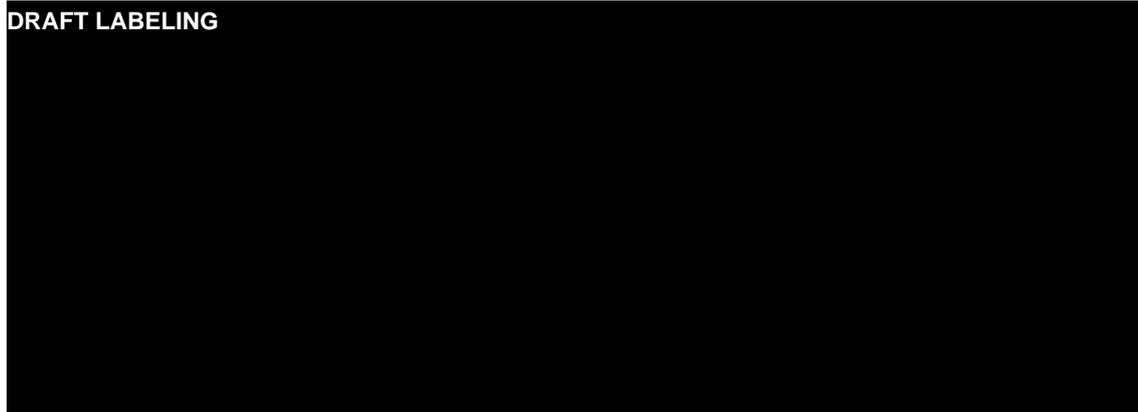
Very few intact PTH concentrations were within the proposed therapeutic range of 150 – 300 pg/ml. For example at the Los Angeles site, only 21 of 53 subjects had iPTH concentrations within the proposed range at 16 weeks, and only 5 or 21 were within the proposed range at 24 weeks, the ends of the 2 treatment phases. Dose adjustment was rampant and PTH concentrations bounced up and down regardless of whether the dosage was changing or not. This indicates that the dose of Hectorol® cannot be titrated to achieve the desired target effect. (See Appendix III) Sometimes iPTH concentrations were extremely low and sometimes extremely high (i.e. in the thousands). Yet the highest dose in the protocol of 20.0 mcg 3 times weekly was only administered to a single subject.

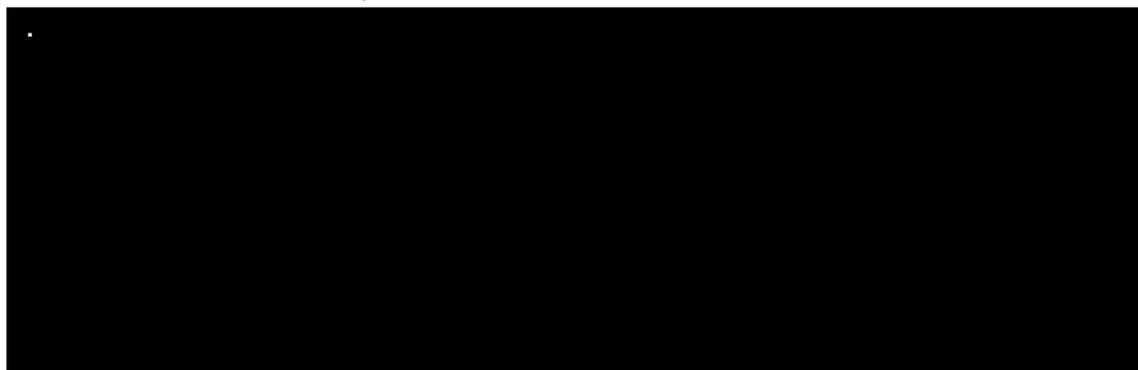
No obvious patterns between dose, vitamin D concentrations and effect on PTH concentrations are apparent. This could be due to the timing of blood samples and the variety of adjustments to dose, as well as unknown adjustments to diet, phosphate binders, and dialysate composition occurring throughout the phase III study. Thus it seems that a much longer study is needed to achieve stable dosing and to achieve stable PTH concentrations and determine a target range. Only population PK/PD modeling might tease out any relationships between concentration and dose or effect.

#### IX. Dosage and Administration

It is suggested that dose be titrated to parathyroid hormone concentration. The dosage and administration section from the proposed professional labeling follows

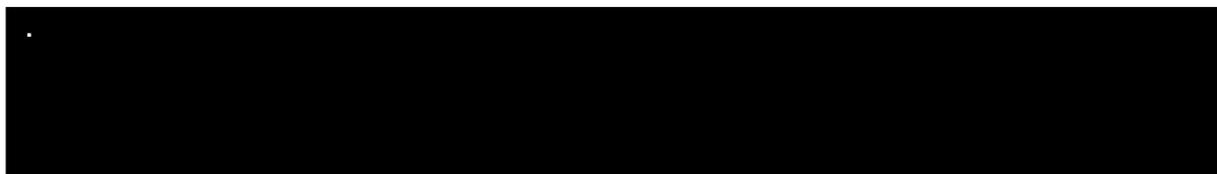
**DRAFT LABELING**



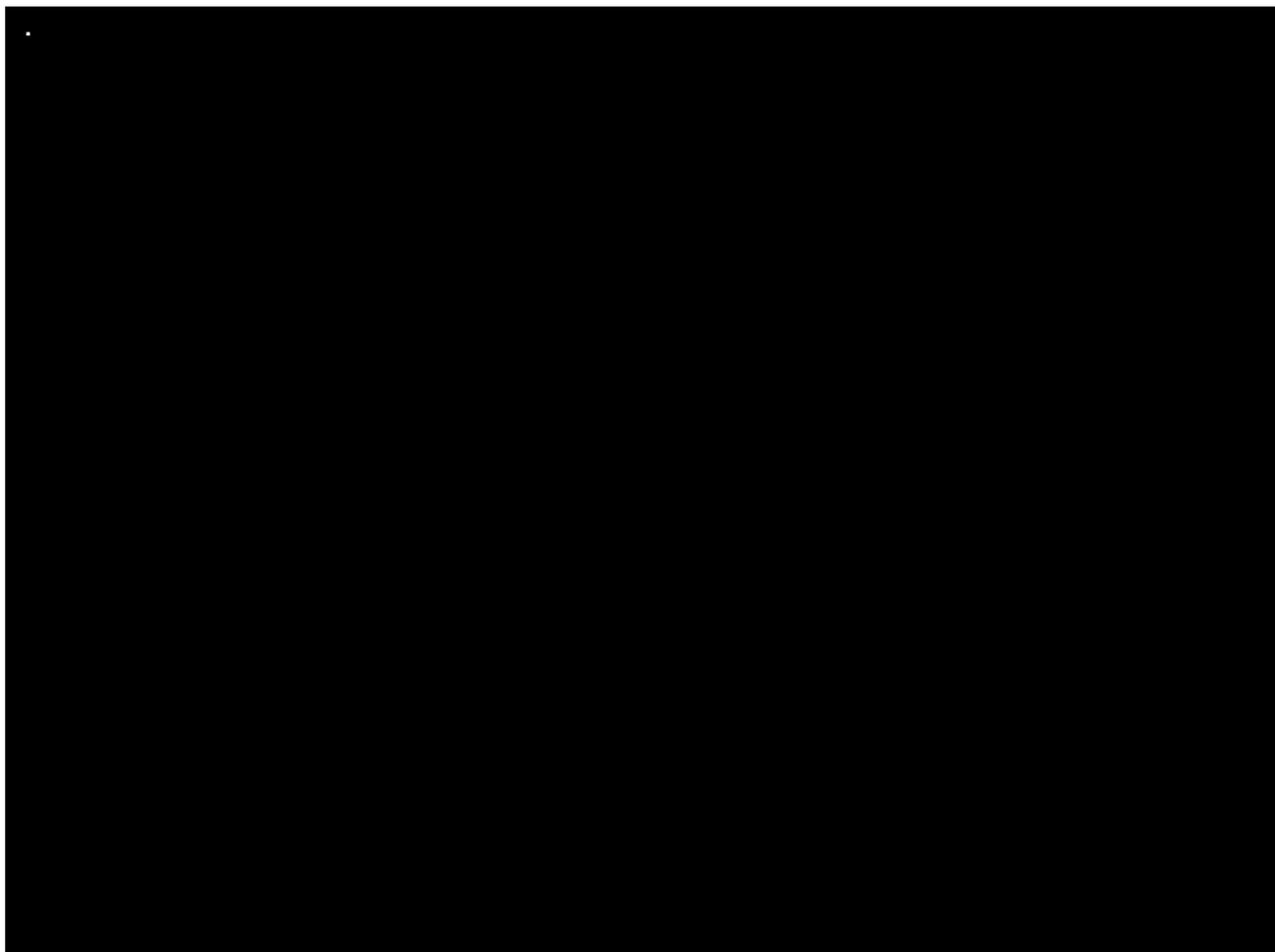


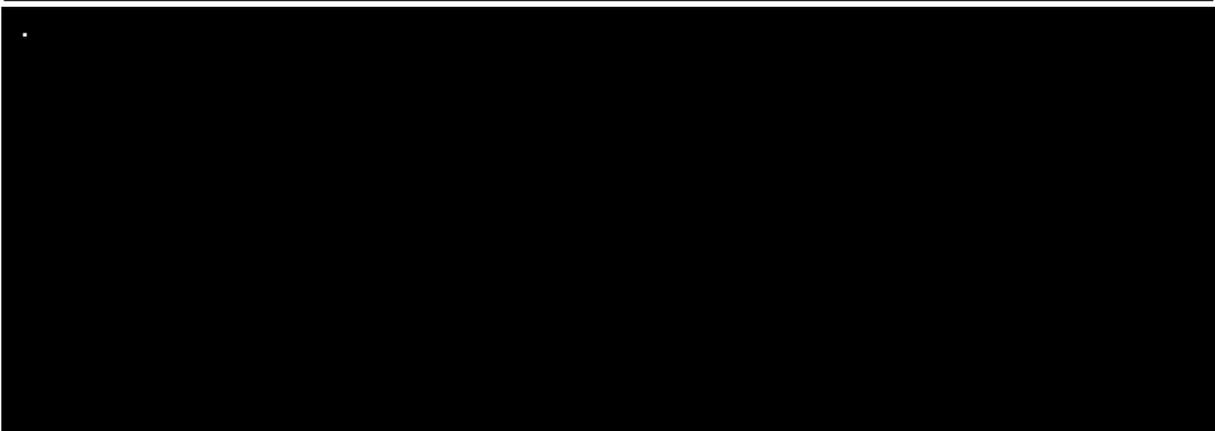
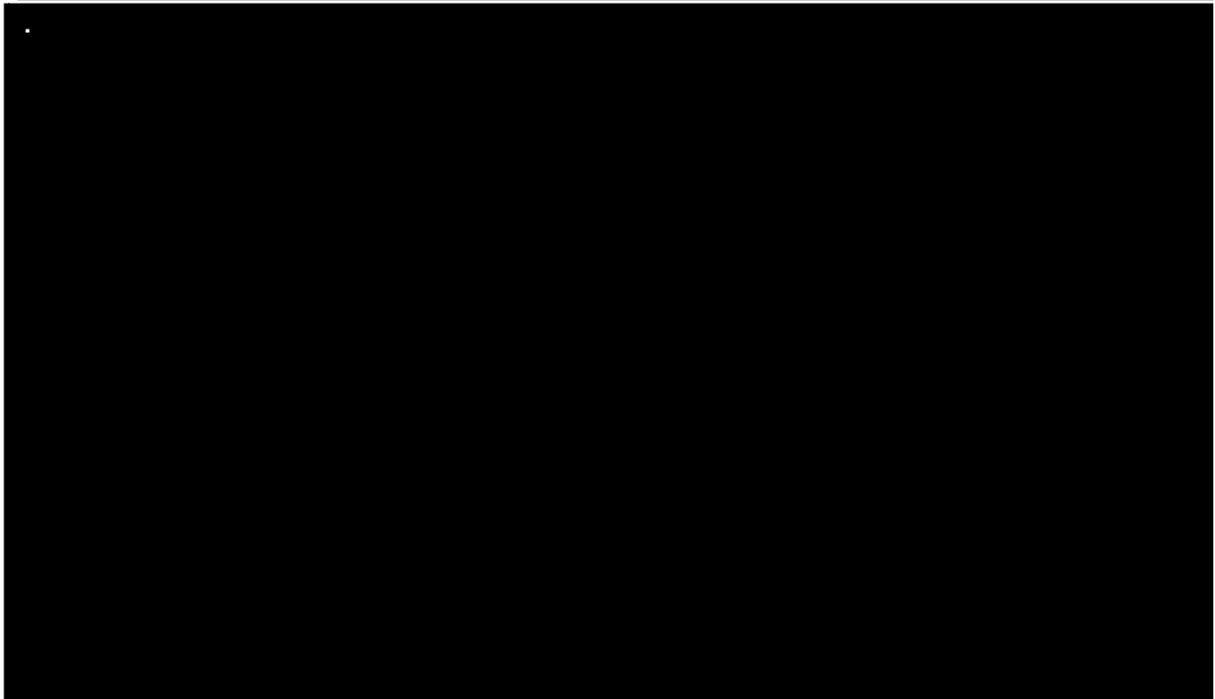
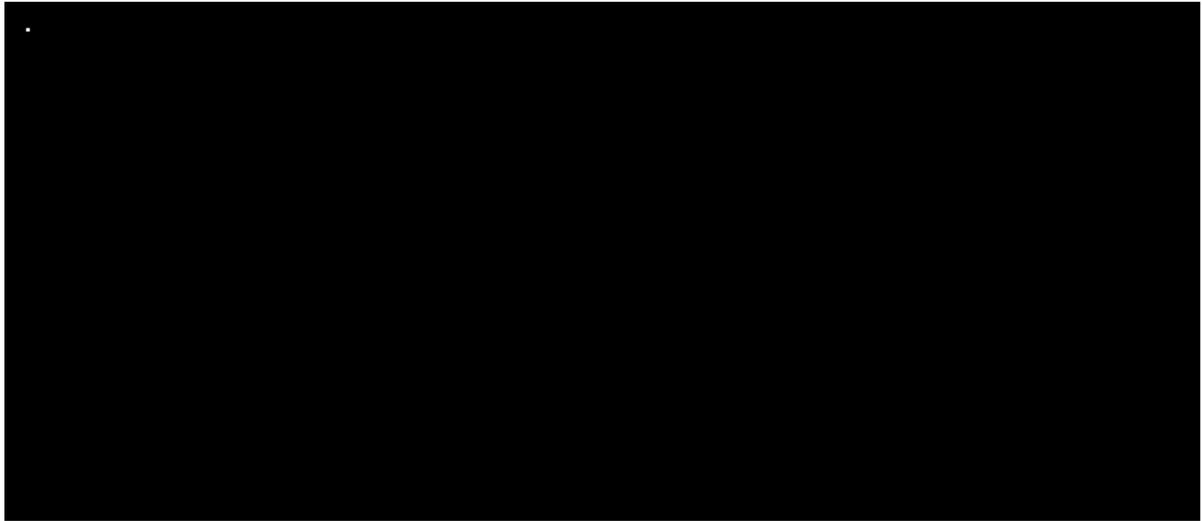
This proposed labeling is inconsistent with the dosing and results of the phase III efficacy studies.

**X. Formulation**



**XI. Dissolution**





**XII. Reviewer Comments to Medical Officer**

The initial phase II study suggests that dosing duration was not long enough to establish a pharmacodynamic equilibrium. In addition the pharmacokinetic study in ESRD suggests that steady-state may not be reached for weeks. Consequently the time interval between dosage adjustments cannot be determined. Data was not presented that supports the recommended target therapeutic range nor was data presented to demonstrate that the therapeutic targets could be consistently achieved in any individual patient.

No obvious patterns between dose, vitamin D concentrations and effect on PTH concentrations are apparent. This could be due to the timing of blood samples and the variety of adjustments to dose, as well as unknown adjustments to diet, phosphate binders, and dialysate composition occurring throughout the phase III study. Based upon this and the phase II study where PTH concentrations were still decreasing after 12 weeks it seems that a much longer study is needed to achieve stable dosing and to achieve stable PTH concentrations and determine dosing recommendations. Only population PK/PD modeling might tease out any relationships between dose, concentration and effect.

A double-blind comparative trial is probably needed to assess the ability to achieve therapeutic targets relative to the currently available vitamin D's. If such a study is performed, subject demographics should be considered, since African-Americans have a lower propensity for postmenopausal osteoporosis they could conceivably be at lower risk for renal osteodystrophy.

It is suggested that Hectorol® be contraindicated in patients with hepatic disease for the following reasons. Hectorol® requires hepatic metabolic activation, plus hepatic disease is expected to potentially effect absorption and elimination with the net effect being unpredictable and potentially variable both between and within patients. In addition there are other Vitamin D compounds that do not require metabolic activation by the liver.

**XIII. Comments to firm**

1. Analytical methods have not been adequately validated. Data provided does not support the claimed lower limit of quantitation and the assay is not sufficiently sensitive to accurately measure concentrations achieved clinically. Consequently all pharmacokinetic and bioavailability data is suspect. Assays should have been validated using the same methods (including calculations) used to determine clinical sample concentrations and should have been validated in the laboratory where the clinical samples are analyzed.

If additional pharmacokinetic data is to be submitted in the future, a method with a reliable and sufficiently low lower limit of quantitation is needed. If feasible, an assay for the parent compound should also be developed.

2. Bioavailability studies should have been performed with assessments of both the parent drug and the active moiety. Ideally dose proportionality should have been assessed within a single study and not across studies and across the entire dosage range.
3. Clinical pharmacology studies in hepatic insufficiency are inadequate as insufficient information is presented. As a fat-soluble vitamin, biliary disease would be expected to have a significant impact on absorption and probably elimination. Subjects that had biliary obstruction or disease should have been identified, and there should have been an assessment as to if there are any

correlation to alterations in pharmacokinetics. If any new reports on the effect of hepatic disease are to be submitted, these should include individual subject clinical and laboratory measures of hepatic disease in addition to composite scales of severity of hepatic disease.

- 4. Other concerns with the hepatic insufficiency study include the inclusion of a subject (#302) receiving cholestyramine. Cholestyramine could have decreased drug absorption and skewed the results in the severely impaired subgroup. There is also a lack of information regarding the effects of associated factors such as ascites and plasma protein concentration. The impact of these factors also need to be assessed. If there are insufficient numbers of subjects to adequately assess the impact of biliary disease and other factors, an additional study may be needed.
- 5. A food effect study with a high fat meal is recommended, since as a fat-soluble vitamin dietary fat is expected to be a significant variable in absorption. Draft guidances are currently available on the internet and may be useful for information purposes.
- 6. Protein binding studies were inadequate as the active species was not studied.
- 7. At this time the FDA holds the sponsor responsible for developing a dissolution method for Hectorol®. The dissolution method proposed by the sponsor is not accepted as it uses the addition of an organic solvent post-disintegration, and other possible methods have not been exhausted. There are several soft gelatin capsule products with an oily fill, that have a dissolution method. The Food and Drug Administration developed some of these methods in their district laboratories. These include the procedures for Danazol, Valproic Acid, Clofibrate and Cycloserine. Various media, apparatus and paddle speeds should be examined. Media to be examined should include use of a surfactant. A number of which are available. One that has been used with success is hexadecyltrimethylammonium bromide (CTAB). Developing a suitable dissolution procedure for soft gelatin capsules with an oily fill is a challenge. However, the sponsor should continue to search for an appropriate dissolution method for Hectorol® capsules.

**XIII. Labeling Comments**

See Attached. (Appendix IV)

**XIV. Signatures**

/s/ [Redacted Signature]

Ronald Evan Kavanagh, B.S. Pharm./Pharm.D., Ph.D.

Division of Pharmaceutical Evaluation II  
Office of Clinical Pharmacology and Biopharmaceutics

RD/HA Initialed by Hae-Young Ahn, Ph.D., Team Leader

/s/ [Redacted Signature] 5/5/99

OCPB Briefing Meeting: March 12, 1999

Attendees: Chen ME, Huang S, Mehta, Lazor J, Ahn H, Kavanagh R, Shore R, Fossler M, Lutwak L, Riley L, Strong J

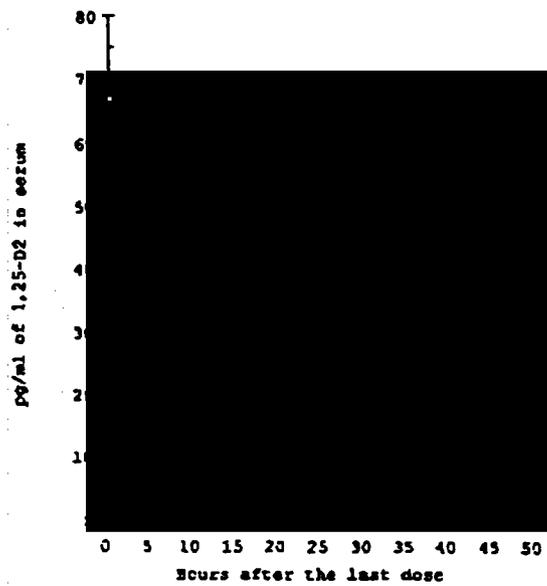
CC: NDA 20-862 (orig., 1 copy), HFD-510(Lutwak, Hedin), HFD-850(Lesko), HFD-870(M. Chen, Kavanagh, Ahn), HFD-340(Vish), Central Document Room (Barbara Murphy)

1/8/99

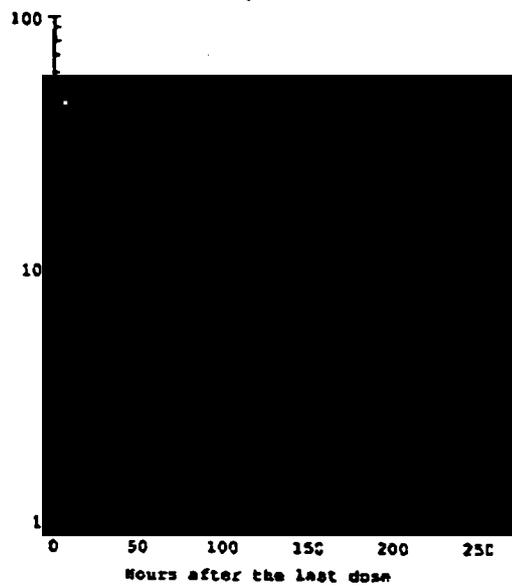
**Appendix I**

**Serum Concentration vs. Time Plots in Subjects with ESRD**

SERUM CONCENTRATIONS OF 1,25-D2  
PATIENT 11  
(Caucasian)



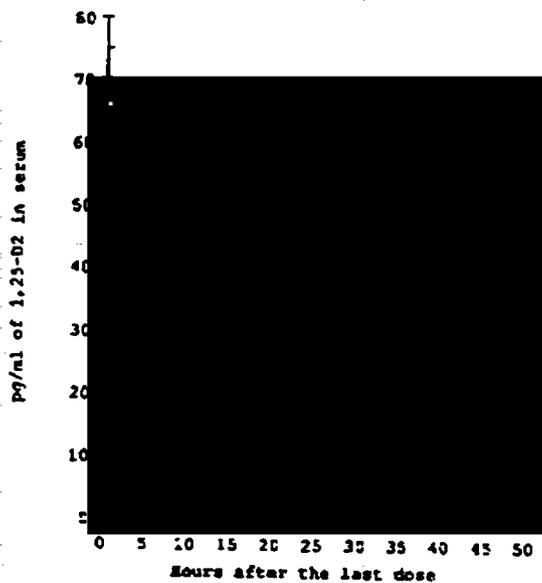
(Semi-logarithmic)



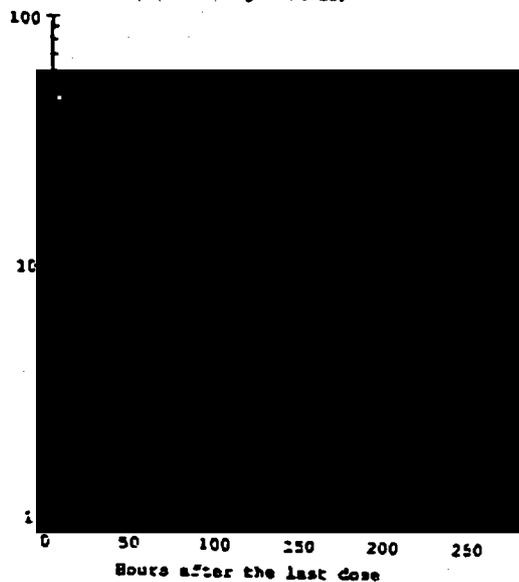
SERUM CONCENTRATIONS OF 1,25-D2

PATIENT 12

(Cartesian)



(Semi-logarithmic)



## Appendix II

### Mean Parathyroid Hormone Concentrations vs. Time

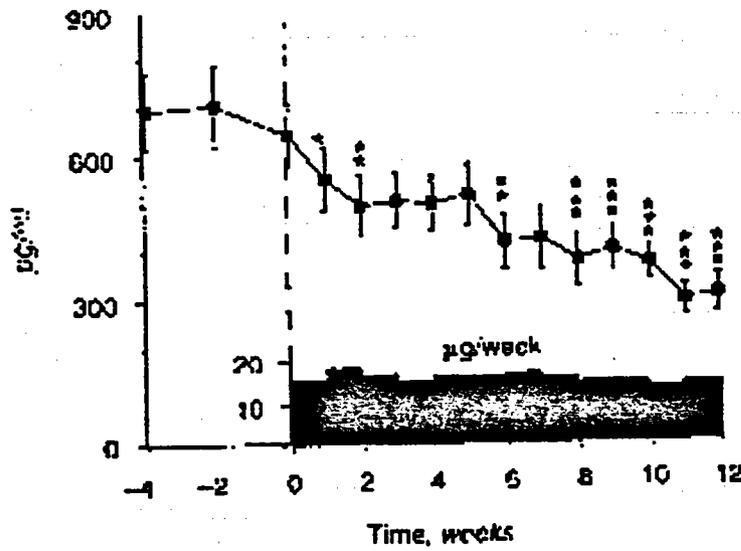


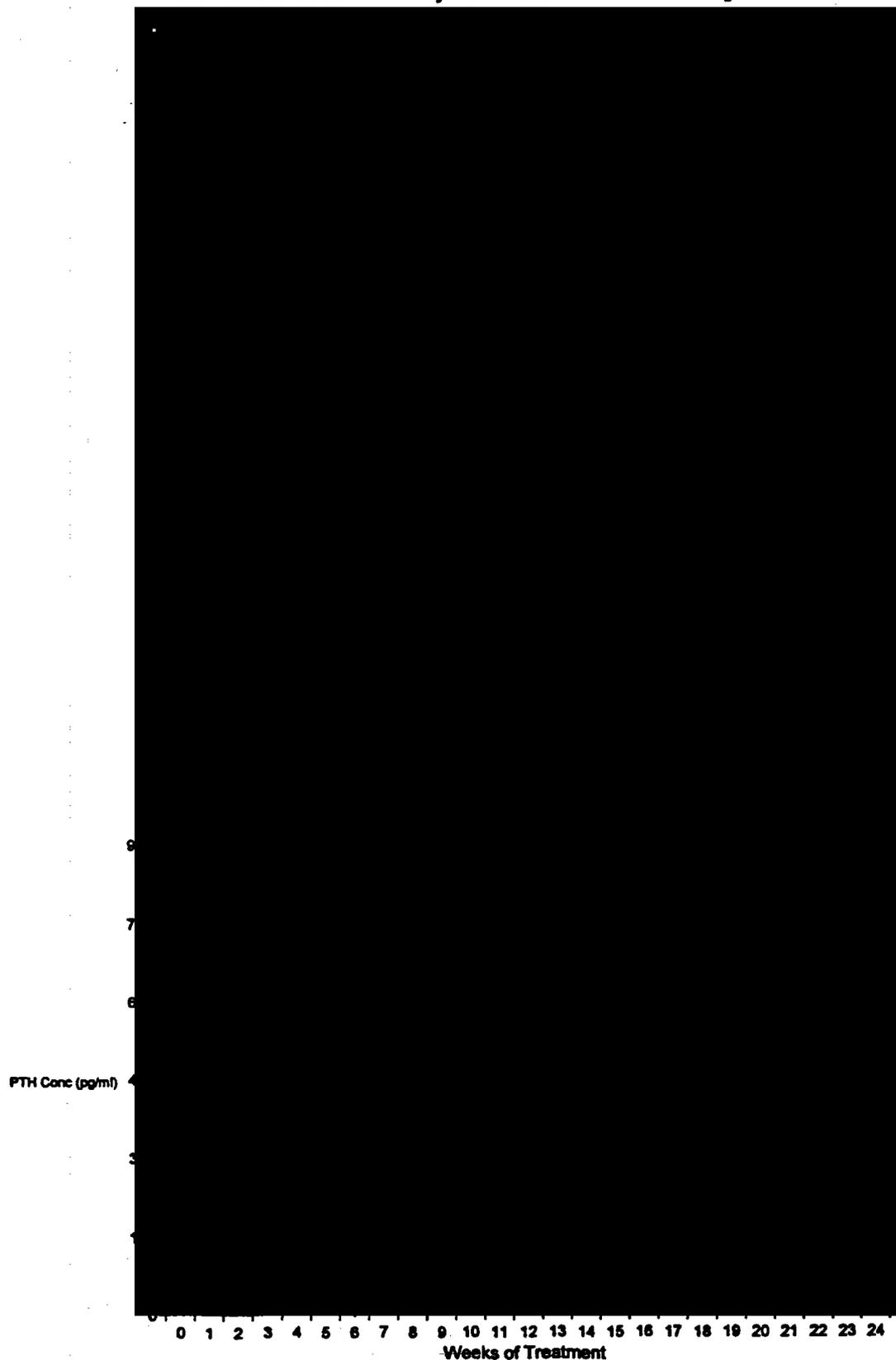
Fig. 3. Mean levels of serum intact PTH during the last four weeks of washout and treatment with 1 $\alpha$ -hydroxy-vitamin D<sub>3</sub> (1 $\alpha$ D<sub>3</sub>), and the mean weekly dosage of 1 $\alpha$ D<sub>3</sub> shown as solid bars. Data are mean  $\pm$  s.e.m. \* values differ from baseline \*P < 0.05; \*\*P < 0.025, and \*\*\*P < 0.01.

APPEARS THIS WAY ON ORIGINAL

**Appendix III**

**PTH Concentrations Achieved with Dose Titration of  
Hectorol®**

PTH Concentration in Subjects Treated with 1 $\alpha$ -OH-D<sub>2</sub> for 24 Weeks



Target Range 150 – 300 pg/ml  
Dose Adjusted at 8 week intervals

**Appendix IV**

**Draft Labeling with Reviewer Comments**

## Sponsor's Annotated Labeling with Editing from OCPB Reviewer

### OCPB Reviewer Comments

n.b. not all comments are currently incorporated into edited labeling. Labeling will need additional editing in consultation with reviewers from other disciplines prior to communication to sponsor.

~~Strikeout text~~ should be removed from the labeling; underlined text should be added.

☛ Indicates additional comments either for explanation, to be discussed internally, or for the sponsor to address.

### CLINICAL PHARMACOLOGY

Calcitriol (1 $\alpha$ ,25 (OH)2D3) and 1 $\alpha$ ,25-(OH)2D<sub>2</sub> ~~precursor~~ regulate blood calcium at levels required for essential body functions, including normal bone growth. Specifically, the active vitamin D metabolites control the intestinal absorption of dietary calcium, the tubular reabsorption of calcium by the kidney and, in conjunction with parathyroid hormone (PTH), the mobilization of calcium from the skeleton. They act directly on bone cells (osteoblasts) to stimulate skeletal growth, and on the parathyroid glands to suppress PTH synthesis and secretion. These functions are mediated by the interaction of these active metabolites with highly specific receptor proteins in the various target tissues. In uremic patients, deficient production of active vitamin D metabolites leads to secondary hyperparathyroidism, the major cause of metabolic bone disease in renal failure [1.5; 014].

After oral administration, 1 $\alpha$ -OH-D<sub>2</sub> is ~~absorbed~~ absorbed from the ~~gastrointestinal tract~~ gastrointestinal tract, and activated by the liver. In healthy volunteers peak blood concentration ~~of~~ of 1 $\alpha$ ,25-(OH)2D<sub>2</sub> are reached at 11-12 hours after repeated oral doses of 5 to 15  $\mu$ g of Hectorol, and the mean half-life of 1 $\alpha$ ,25-(OH)2D<sub>2</sub> elimination is approximately 32 to 37 hours with a range of up to 96 hours. [1.26; 004] The half-life in subjects with ESRD on dialysis appears to be similar. ~~\_\_\_\_\_~~

\_\_\_\_\_ causes a temporary increase in 1 $\alpha$ -OH-D<sub>2</sub> concentrations (46% increase in mean postdialysis concentrations compared to mean predialysis concentrations). This temporary increase is presumably due to volume contraction.

☛ Remove rapidly and change the site of absorption. No data is provided on the rate or site of absorption.

☛ Elimination half-life is approximately 32 to 37 hours in healthy volunteers. Data from subjects with ESRD on dialysis appears similar or slightly higher if post dialysis concentrations are excluded.

### Food Effects

Food effect studies have not been conducted with Hectorol® soft gelatin capsules. Since Hectorol® is a fat soluble vitamin food effects are expected, especially with fats. The nature and magnitude of any potential food effects on the rate and extent of absorption are unpredictable

A food effect with nonabsorbable synthetic fat substitutes is expected to decrease the absorption of Hectorol®.

### WARNINGS

☛ Comment for Medical Officer's Consideration:

Would the presence of certain cardiac arrhythmia's, and seizure disorders be effected by alterations in calcium concentrations and is there is any need to include these in the warnings section?

### PRECAUTIONS

#### Information for the Patient

The patient, spouse, or guardian should be informed about compliance with dosage instructions, adherence to instructions about diet and calcium supplementation and avoidance of the use of unapproved nonprescription drugs.

Patients should also be carefully informed about the symptoms of hypercalcemia (see ADVERSE REACTIONS section) [1.42; 126-127].

☛ **Comments for Medical Officer's Consideration:**

The sponsor needs to expand on this section. nonprescription drugs need to be specified as to type, e.g. antacids containing aluminum, calcium, or magnesium, and calcium supplements; lipophilic substances such as mineral oil, castor oil, MCT and cod liver oil that can effect absorption may need to be added. Drugs high in phosphates, e.g. Fleet® enema, also need to be included. See comments on drug interactions.

**Drug Interactions**

Cholestyramine has been reported to reduce intestinal absorption of fat-soluble vitamins; as such it may impair intestinal absorption of 1<sub>α</sub>-OH-D<sub>2</sub>. Magnesium-containing antacid and Hectorol should not be used concomitantly, because such use may lead to the development of hypermagnesemia. (Also see WARNINGS and PRECAUTIONS [General] sections.) [1.42; 126].

☛ **Comments for Medical Officer's Consideration:**

Although no specific drug interaction studies have been performed. Certain classes of drugs are predicted to have drug interactions with Hectorol®. The sponsor should address these potential interactions.

Since 1<sub>α</sub>-OH-D<sub>2</sub> is a fat soluble vitamin it is expected that drugs that impair or enhance the absorption of fats may decrease the absorption of Hectorol. It is also expected that drugs that alter bile acid secretion may also alter both the absorption and elimination of Hectorol. The net effect on Hectorol absorption and systemic exposure is thus unpredictable and patients should be monitored closely.

The following drugs might effect Hectorol® absorption:

Lipophilic substances such as mineral oil, castor oil, Medium Chain Triglycerides (MCT) and cod liver oil.

Cholestyramine may inhibit Hectorol® absorption.

Docusate sodium.

Nonabsorbable dietary fat substitutes, such as Olestra®.

GI lipase inhibitors may also need to be added if any come to market.

Colestipol an anion exchange resin may alter Hectorol® absorption indirectly as it binds bile acids.

Aluminum based antacids absorb bile acids *in vitro* consequently they may alter Hectorol® absorption indirectly.

The effect of ursodiol on Hectorol pharmacokinetics is unknown since it does not effect bile acid metabolism but does effect cholesterol metabolism.

Since Hectorol is both metabolically activated and metabolically eliminated both enzyme inducers and inhibitors may effect the dose of Hectorol that a patient receives. Consequently they should be used cautiously with Hectorol®.

Some enzyme inducers such as glutethimide, phenytoin and phenobarbital have been reported to induce the metabolism of other vitamin D's and may have similar effects on Hectorol®. In addition phenytoin may inhibit the 25-hydroxylation of vitamin D's. Consequently dosage adjustment may be necessary when administered concurrently.

Ketoconazole has been shown to inhibit the elimination of calcitriol via metabolic inhibition, consequently inhibition of Hectorol® elimination is likely.

Hectorol® is expected to interact with drugs that may increase calcium or magnesium concentrations.

Antacids containing Aluminum, Calcium, or Magnesium, and calcium supplements should be used

cautiously in patients receiving Hectorol®.

Magnesium salicylate.

Other vitamin D's analogues should not be administered concurrently with Hectorol®.

Concomitant thiazide use may cause hypercalcemia and should be used cautiously.

Hectorol® should be used cautiously in patients receiving drugs whose actions may be mediated through their effects on calcium, including calcium channel antagonists or whose effects may be modulated by calcium concentrations e.g. digitalis glycosides.

Drugs with high phosphate concentrations should be used with caution in patients with end stage renal disease. These including phosphate enemas and laxatives such as Fleets enema and Milk of Magnesia.

#### Nursing Mothers

It is not known whether this drug is excreted in human milk—

Vitamin D<sub>2</sub> has been reported in human breast milk at concentrations 8400 fold greater than normal concentrations in a woman receiving pharmacologic doses, i.e. 100,000 IU of vitamin D<sub>2</sub>. Due to the structural similarity of Hectorol® to vitamin D<sub>2</sub> and the potential for serious adverse reactions in nursing infants from 1<sub>α</sub>-OH-D<sub>2</sub>, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Ref: J Pediatrics July 1984: 105(1) 61-63

#### Hepatic Insufficiency

Studies in subjects with hepatic disease were not able to provide adequate information on the effects of various types or severity of hepatic disease. Hectorol® is a fat soluble vitamin that is activated by the liver and eliminated in the bile. Consequently hepatic insufficiency and/or alterations in bile acid metabolism or secretion is expected to potentially alter absorption, activation, and elimination. Since these alterations may have opposing effects on Hectorol® plasma concentrations the net effect is unpredictable and Hectorol® should be administered with caution in patients with hepatic disease, especially those with alterations of bile acid production or elimination.

#### OVERDOSAGE

Administration of Hectorol to patients in excess of their daily requirements can cause hypercalcemia, hypercalciuria, hyperphosphatemia, and over-suppression of parathyroid hormone secretion leading in certain cases to adynamic bone disease [1.42; 126]. High intake of calcium and phosphate concomitant with Hectorol may lead to similar abnormalities. High levels of calcium in the dialysate bath may contribute to the hypercalcemia.

#### Treatment of Hypercalcemia and Overdosage

General treatment of hypercalcemia (greater than 1 mg/dL above the upper limit of the normal range) consists of immediate discontinuation of Hectorol therapy, institution of a low calcium diet, and withdrawal of calcium supplements. Serum calcium levels should be determined at least weekly until normocalcemia ensues. Hypercalcemia usually resolves in 2 to 7 days. When serum calcium levels have returned to within normal limits, Hectorol therapy may be reinstated at a dose which is 2.5 mcg lower than prior therapy. Serum calcium levels should be obtained weekly after all dosage changes and during subsequent dosage titration. Persistent or markedly elevated serum calcium levels may be corrected by dialysis against a reduced calcium or calcium-free dialysate [1.42; 124].

#### Treatment of Accidental Overdosage of 1<sub>α</sub>-OH-D<sub>2</sub>

The treatment of acute accidental overdosage of Hectorol should consist of general supportive measures. If drug ingestion is discovered within a relatively short time, induction of emesis or gastric lavage may be of benefit in preventing further absorption. If the drug has passed through the stomach, the administration of mineral oil may promote its fecal elimination. Serial serum electrolyte determinations (especially calcium), rate of urinary calcium excretion, and assessment of electrocardiographic abnormalities due to hypercalcemia should be obtained. Such monitoring is critical in patients receiving digitalis. Discontinuation of supplemental calcium and a low calcium diet are also indicated in accidental overdosage.

Should, however, persistent and markedly elevated serum calcium levels occur, there are a variety of therapeutic alternatives which may be considered, depending on the patient's underlying condition. These include the use of drugs such as phosphates and corticosteroids as well as measures to induce an appropriate forced diuresis. Dialysis against a calcium-free dialysate has also been reported [1.42; 124].

**☛ Comments for the Medical Officer's Consideration:**

If the drug has passed through the stomach, the administration of mineral oil may promote its fecal elimination

Toxindex® recommends that charcoal should be administered for vitamin D overdoses of 100X the RDA.

Hemodialysis is not expected to eliminate Hectorol® or its' active metabolites from the body.

**DOSAGE AND ADMINISTRATION****Adult Administration:**

The optimal dose of Hectorol must be carefully determined for each patient [1.42; 112-114].

The recommended initial dose of Hectorol is 10.0 mcg administered three times weekly after 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 2.5 - 5.0 mcg if PTH is not lowered by 50% and fails to reach the target range. Drug administration should be suspended if PTH falls below 150 pg/mL and restarted one week later at a dose which is 2.5 mcg lower. During titration, PTH, serum calcium, and phosphorus levels should be obtained weekly. If hypercalcemia, hyperphosphatemia, or a serum calcium times phosphorus product greater than 70 is noted, the drug should be immediately discontinued until these parameters are appropriately lowered. Then, the drug should be restarted at a dose which is 2.5 mcg lower.

Incremental dosing must be individualized and commensurate with PTH, serum calcium and phosphorus levels. The following is a suggested approach in dose titration:

PTH Level	Hectorol Dose	
400 pg/mL	10.0 mcg three times per week after dialysis, or approximately every other day	
Decreased by < 50% and above 300 pg/mL	Increase every eight weeks by 2.5 to 5.0 mcg	Need maximum dosage. Same as per clinical trials.
50 - 300 pg/mL	Maintain	
< 150 pg/mL	Suspend for one week, then resume at a dose which is 2.5 mcg lower	

**☛ Comments for the Medical Officer's Consideration:**

A maximum dose is needed. In the clinical trials the maximum dose was 20 mcg 3 times weekly, however only 1 subject was treated at this dose level. In addition, few subjects (approximately 5 -10) were treated at 15 mcg 3 times weekly, and only 1 or 2 subjects at 12.5 mcg. Consequently we need to consider if sufficient numbers of subjects are evaluable at these dose levels for safety and efficacy purposes.

**APPEARS THIS WAY ON ORIGINAL**