CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-027

MEDICAL REVIEW(S)

MEDICAL TEAM LEADER REVIEW

OF NDA 21-027

HECTOROL™
DOXERCALCIFEROL INJECTION

SPONSOR: Bone Care International

INDICATION: Management of secondary hyperparathyroidism

DATE SUBMITTED: 12/20/1999

DATE REVIEWED: 02/03/2000

PRIMARY MEDICAL REVIEWER: Leo Lutwak, M.D., Ph.D.

Administrative Background

The oral (capsule) formulation of Hectorol was approved by the Agency for the management of secondary hyperparathyroidism in June 1999. Following the submission of NDA [redacted] the review division considered the application "non-filable". Doctor Lutwak, the primary medical reviewer for Hectorol, had concerns about the design of study H-114 (primary study for the IV formulation) and study H-108 (primary study for the oral formulation and the study from which patients were enrolled into H-114). Despite the Division's refusal to file NDA [redacted] the application was eventually "filed over protest" by Bone Care International.

Clinical Study Background

The approval of the oral formulation of Hectorol was based primarily on studies H-108-LA and H-108-Memphis. Although reported as two separate studies, the same protocol was used for both investigations and the only substantive difference between the studies was location. Study H-108-LA was conducted at multiple dialysis centers in the greater Los Angeles area, and H-108-Memphis was conducted at multiple dialysis centers in the greater Memphis area.

Protocol H-114, the primary basis for approval of the IV Hectorol formulation, was originally designed as a double-blind, placebo-controlled study. According to Bone Care International, the FDA suggested that study H-114 be re-designed as a crossover extension to protocol H-108. The company agreed to this change and re-submitted the protocol, which was approved by the Division in June of 1997.

To gain a full appreciation of study H-114, one must briefly examine the design of and patient disposition in study H-108.

Study Flow and Patient Disposition in Protocol H-108

This study of end stage renal disease patients with secondary hyperparathyroidism began with an 8-week washout period (Week –8). During this time subjects were instructed to avoid taking any vitamin D therapy. At Week 0, patients entered into a 16-week period during which time they received open-label treatment with oral Hectorol. At Week 16, subjects were then randomized into an 8-week double-blind, placebo-controlled period during which time half the patients continued to receive oral Hectorol and half received matching placebo.

Two hundred and eleven patients were enrolled into the 8-week washout period. Seventy-three subjects were either disqualified or discontinued during this time and thus 138 patients entered the 16-week open-label portion of the study. A total of 16 participants discontinued therapy during the open-label period; this left 122 patients who were randomized into the double-blind portion of the study. Twelve subjects discontinued from the study during this 8-week period, leaving 110 subjects. Only 99 patients were considered evaluable by the sponsor because 11 participants received additional vitamin D treatment or had other protocol evaluations. Thus, of the 211 patients enrolled into study H-108, 110 subjects completed the study and 99 were considered evaluable. Therefore, all of the patients who were eligible for study H-114 completed and came from study H-108.

Reviewer Comment: Fifty-two percent of the subjects enrolled into H-108 completed the 32-week study. While this represents a high dropout rate, it is not unexpected given the patient population and their propensity for co-morbid illness, hospitalization, and significant metabolic disturbances.

Crossover from study H-108 to study H-114

As mentioned above, it was the intention of the sponsor to immediately crossover patients who completed study H-108 (oral Hectorol) into H-114 (IV Hectorol). However, an adequate supply of IV Hectorol was not available until six months after the first subjects had completed study H-108. Subjects awaiting re-enrollment into study H-114 received other forms of vitamin D treatment as needed during the intervening period.

Reviewer Comment: Because subjects received alternative forms of vitamin D during this period and underwent a wash-out phase prior to treatment with IV Hectorol, it is unlikely that the unplanned delay in treatment with IV Hectorol significantly affected the outcome of the study.

Clinical Study Section

In the following section, data from the dialysis centers in Los Angeles and Memphis will be reviewed as separate studies.

Study H-114 Memphis

This study was conducted between July 16, 1997 and December 30, 1997 in 8 community-based dialysis units.

Primary Objectives: To assess the efficacy (serum iPTH) and safety (serum Ca and Phos) of pulse doses of IV Hectorol as a therapy for secondary hyperparathyroidism in patients with end stage renal disease on hemodialysis.

Study Design: Although this study was intended to be conducted as a crossover extension of study H-108, there was at least a 6 month delay from the time study H108 was completed until patients enrolled into H-114. Patients who entered this study completed an 8-week washout period followed by 12-weeks of open-label treatment with IV Hectorol. During the washout period patients were taken off all vitamin D therapies. Throughout the washout and open-label treatment periods, patients underwent hemodialysis (3 times per week) using a 2.0-3.5 mEq calcium dialysate. The initial dose of IV Hectorol was 4.0 ug administered after each hemodialysis treatment. The dose was adjusted to bring plasma iPTH levels into the

target range of 150 to 300 pg/mL. The maximum dosage of Hectorol was limited to 6 ug per hemodialysis session.

Patients who developed a serum Ca level of > 11.2 mg/dl or a serum Phos level of > 8.0 mg/dl (on two consecutive occasions), or a Ca x Phos product of > 75 for 3 consecutive weeks had their dose of Hectorol suspended. Serum levels were monitored at each dialysis session until the Ca was ≤ 10.5 mg/dl, or the Phos was ≤ 6.9 mg/dl, or the Ca x Phos was ≤ 70 after which they resumed Hectorol at one reduced dose level ***Reviewer Comment: an algorithm was followed by the investigators to ensure consistent alterations in dosing in response to variations in levels of serum Ca, Phos, and iPTH.*** When a patient developed mild elevations in serum Ca or Phos (Ca > [redacted] mg/dl and Phos [redacted] mg/dl) they were instructed to adjust their consumption of calcium-based phosphate binders and/or reduce their test drug dosage by one level. Patients whose plasma iPTH levels fell below 150 pg/ml immediately suspended treatment and then resumed test drug dosing at one level lower than previously administered at the mid-week dialysis session of the following week.

At the investigator's discretion, the dosage of calcium-based dietary phosphate binders was adjusted up or down to correct for moderate hyperphosphatemia ([redacted] mg/dl) or mild hypercalcemia (> [redacted] mg/dl). In the case of persistent (3 consecutive weeks) mild hypercalcemia and hyperphosphatemia when phosphate binders could not be adjusted, or a serum Ca x Phos product was > 70, the dosage of Hectorol was reduced to a rate of one level below the previous dose.

Patient Population: Patients qualified for inclusion in this study if they completed study H-108 (oral Hectorol) and were evaluable for statistical purposes. Subjects who discontinued prematurely from study H-108 after Week 16 because of concomitant use of calcitriol were allowed to participate in this study if they met the other eligibility criteria.

Inclusion criteria included:

- Aged 20 to 75 years
- Had been on hemodialysis for at least 4 months
- Had an average serum Phos in the range of 2.5 to ≤ 6.9 mg/dl during the 2 months prior to enrolling in study H-108
- Had a history of elevated iPTH (> 400 pg/ml) when not receiving vitamin D therapy
- Had a normal or minimally reduced average serum albumin during the previous two months (not lower than 0.5 g/dL below the normal range)

Exclusion criteria included:

- Having undergone partial or total parathyroidectomy after completing H-108
- Having a serum aluminum level of > 40 ng/ml

The following patients were precluded from entering the 8-week treatment period

- Subjects who failed to exhibit an average serum phosphorus in the range of 2.5 to ≤ 6.9 mg/dl during the washout period
- Subjects who failed to exhibit an average serum calcium of ≤ 10.5 mg/dl during the washout period
- Subjects who failed to have an average Ca x Phos product of ≤ 70 during the washout period
- Subjects who switched to ambulatory peritoneal dialysis
- Subjects who did not have at least one iPTH value above 400 pg/ml during the first 7 weeks of the washout period

Endpoints: The primary efficacy endpoint was the level of serum iPTH. Serum iPTH levels were measured weekly using a [redacted]. The primary safety endpoints were the levels of serum Ca and Phos. These parameters were also measured weekly. Routine chemistries were measured every 4 weeks.

Statistical Analyses: The sponsor defined evaluable subjects as follows: the subject maintained an average serum Phos in the range of 2.5 to ≤ 6.9 mg/dl during the treatment period; the subject received at least 80%

of the test drug; the subject did not receive calcitriol or aluminum-containing products during the study; and analysis of the subject's plasma confirmed a circulating level of 1-alpha, 25-$(OH)_2D_3$ that was consistent with the prescribed dosage of test drug.

Baseline values for serum Ca, Phos, and iPTH were defined as the average of the data collected during the last three visits during the washout period. The sponsor defines two Intent-to-Treat analyses: 1) all subjects who received test medication, and 2) all subjects enrolled whether or not they received test medication. Per protocol analyses included data on those subjects who completed the study and were evaluable for statistical purposes.

The significance of the change in the efficacy and safety parameters from baseline to Endpoint was determined using a paired t-test. Paired t-tests were also used to compare, at comparable times points, the mean value of the efficacy and safety parameters in H-108 and H-114.

Results

Patient Disposition: A total of 61 subjects were eligible for enrollment into the washout phase. Four of these subjects declined to participate in the study. Of these 57 patients, 15 did not meet the criteria for entrance into the open-label treatment phase: 7 subjects did not have iPTH levels > 400 pg/dl; 3 subjects had increased levels of serum Phos (>6.9 mg/dl); 1 subject was discontinued during the washout phase for receipt of aluminum-containing phosphate binders; 1 subject was discontinued after receiving calcitriol for the third time; and 3 patients died during the washout period. Therefore, 42 subjects entered and completed the open-label treatment phase.

Protocol Violations: Although unlikely to have significantly affected the efficacy results, two protocol violations merit mention. Subject 16101 was discovered, post study completion, to have inadvertently received a single dose of calcitriol in the third week of the treatment period. And subject 18109 was inadvertently dosed with the test drug after dialysis on what was scheduled to be the final study visit.

Patient Demographics: In addition to the demographic characteristics for the subjects enrolled into the open-label phase of this study, the following table provides the patient demographic profiles for the subjects enrolled into the open-label phase of study H-108.

Demographic Characteristic	H-108 (n=76)	H-114 (n=42)
Mean Age (range) (yrs)	(27-75)	51 (28-76)
% Male	45%	48%
% Black	99%	100%
% Caucasian	1.3%	0%
Serum iPTH (pg/ml)	981.5	762.2
Serum Ca (mg/dl)	9.04	9.04
Serum Phos (mg/dl)	4.89	5.03
Mean # Months on Dialysis	55.6	61

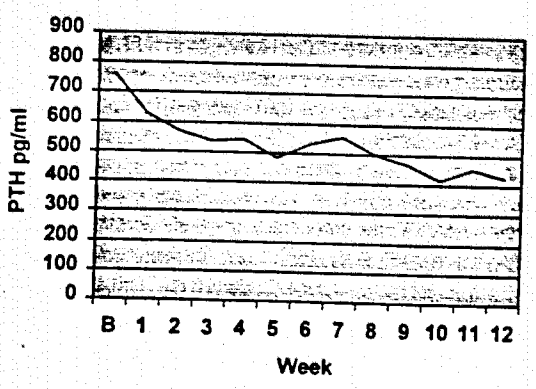
Mean Weekly Drug Dosage and Compliance: The mean weekly drug dosage ranged from 9.12 ug to 11.62 ug. As expected in a trial where study drug is administered at dialysis sessions, compliance was very high: on average 99%.

Primary Efficacy Outcome

Serum iPTH Levels (per protocol)

The mean serum iPTH level at baseline was 774 pg/ml (range [redacted] pg/ml). At Week 12, the mean iPTH level was reduced to 428 pg/ml ($p<0.001$). Results from the ITT analysis were similar. As shown in the figure below, the iPTH levels tended to decrease gradually over the 12-week treatment period. It is worth noting that a plateau was not reached by Week 12.

Mean Weekly PTH Levels



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Compared to baseline, the mean values for iPTH during Weeks 1-12 were statistically significantly lower ($p<0.001$).

Ninety-three percent of the subjects achieved a iPTH suppression of $\geq$ 30% on or before Week 10. The average dose of IV Hectorol required to achieve $\geq$ 30% iPTH suppression was 3.9 ug per dialysis session.

Eighty percent of the subjects reached the pre-determined targeted iPTH range of 150 – 300 pg/ml one at least one occasion during the study. Fourteen of 42 patients had iPTH levels below 300 pg/ml on greater than 3 consecutive occasions.

Primary Safety Outcomes

Serum Calcium Levels (per protocol)

The mean serum Ca level at baseline was 9.0 mg/dl. At Week 12 the mean Ca level had increased by 0.6 mg/dl ($p=0.001$). Results from the ITT analysis were similar. This increase of 0.6 mg/dl was the same as that seen during 12 weeks of therapy with oral Hectorol in study H-108. Importantly, the mean level of serum albumin did not change significantly from baseline to Week 12. The maximum serum Ca level recorded during the study was 12.6 mg/dl.

Episodes of Hypercalcemia

Hypercalcemia was defined as a level > 11.2 mg/dl. There were 5 episodes of hypercalcemia in 5 subjects during the 12-week study period (1 episode/100 patient weeks). This incidence of 1.0 episodes/100 patient weeks during treatment with IV Hectorol compares to 2.6 episodes/100 patient weeks with oral Hectorol.

Serum Phosphorus Levels (per protocol)

The mean serum Phos level at baseline was 5.0 mg/dl. At Week 12 the mean Phos level was 6.0 mg/dl ($P<0.001$). Results from the ITT analysis were similar. For comparison, during the 16-week open label portion of the oral Hectorol study the mean Phos level increased from 4.8 mg/dl at baseline to 5.5 mg/dl. The maximum serum Phos level recorded during the study was 10.3 mg/dl.

Episodes of Hyperphosphatemia

Hyperphosphatemia was defined a level > 8.0 mg/dl. There were 19 episodes in 15 patients during the 12-week study period (3.7 episodes/100 patient weeks). This incidence of 3.7 episodes/100 patient weeks during treatment with IV Hectorol compares to 5.2 episodes/100 patient weeks with oral Hectorol.

1alpha ,25-$(OH)_2D_2$ Levels

Predialysis levels of 1alpha, 25-$(OH)_2D_2$ (the active metabolite of Hectorol) were below the limit of detection [redacted] in most of the subjects at baseline. The average level of 1alpha, 25-$(OH)_2D_2$ at baseline was 5.2 pg/ml. At Week 12 the mean level had increased to 20.0 pg/ml ($p<0.001$). For comparison, in H-108-Memphis, the mean level of 1alpha, 25-$(OH)_2D_2$ increased from 5.1 pg/ml at baseline to 33.8 pg/ml at Week 12.

Serious Adverse Events

No patient died during treatment with IV Hectorol. Four patients had 4 serious adverse events during the 12-weeks of treatment with IV Hectorol. During Week 0, a subject had a carotid occlusion that required hospitalization. Also during Week 0, another patient had a possible TIA. During Week 4, a participant was hospitalized for SOB and chest pain. Cardiac enzymes were negative. The final serious adverse event occurred during Week 5; the patient was hospitalized for severe chest, arm, leg, and abdominal pain. The subject was diagnosed with a non-Q wave MI and discharged after 6 days.

Sponsor's Conclusions

This study demonstrates that 1 alpha-OH-D_2, when given intravenously, three times a week, is efficacious and safe in lowering plasma levels of iPTH in patients with moderate-to-severe-secondary hyperparathyroidism associated with ESRD. The results of this protocol as compared with Protocol No. H-108 support the conclusion that intravenous 1 alpha-OH-D_2 is similar in efficacy and safety to the oral formulation of 1 alpha-OH-D_2. Both formulations have demonstrated they are an efficacious and safe alternative to calcitriol in uremic subjects with secondary hyperparathyroidism.

Study H-114 Los Angeles

This study was conducted between July 2, 1997 and February 11, 1998 in 8 community-based dialysis units in the greater Los Angeles area.

Primary Objectives: To assess the efficacy (serum iPTH) and safety (serum Ca and Phos) of pulse doses of IV Hectorol as a therapy for secondary hyperparathyroidism in patients with end stage renal disease on hemodialysis.

Study Design: Although this study was intended to be conducted as a crossover extension of study H-108, there was at least a 6 month delay from the time study H108 was completed until patients enrolled into H-114. Patients who entered this study completed an 8-week washout period followed by 12-weeks of open-label treatment with IV Hectorol. During the washout period patients were taken off all vitamin D therapies. Throughout the washout and open-label treatment periods, patients underwent hemodialysis (3 times per week) using a 2.0-3.5 mEq calcium dialysate. The initial dose of IV Hectorol was 4.0 ug administered after each hemodialysis treatment. The dose was adjusted to bring plasma iPTH levels into the target range of 150 to 300 pg/mL. The maximum dosage of Hectorol was limited to 6 ug per hemodialysis session.

Patients who developed a serum Ca level of > 11.2 mg/dl or a serum Phos level of > 8.0 mg/dl (on two consecutive occasions), or a Ca x Phos product of > 75 for 3 consecutive weeks had their dose of Hectorol suspended. Serum levels were monitored at each dialysis session until the Ca was ≤ 10.5 mg/dl, or the Phos was ≤ 6.9 mg/dl, or the Ca x Phos was ≤ 70 after which they resumed Hectorol at one reduced dose level ***Reviewer Comment: an algorithm was followed by the investigators to ensure consistent alterations in dosing in response to variations in levels of serum Ca, Phos, and iPTH.*** When a patient developed mild elevations in serum Ca or Phos (Ca [redacted] mg/dl and Phos [redacted] mg/dl) they were instructed to adjust their consumption of calcium-based phosphate binders and/or reduce their test drug dosage by one level. Patients whose plasma iPTH levels fell below 150 pg/ml immediately suspended treatment and then resumed test drug dosing at one level lower than previously administered at the mid-week dialysis session of the following week.

At the investigator's discretion, the dosage of calcium-based dietary phosphate binders was adjusted up or down to correct for moderate hyperphosphatemia [redacted] mg/dl) or mild hypercalcemia [redacted] mg/dl). In the case of persistent (3 consecutive weeks) mild hypercalcemia and hyperphosphatemia when phosphate binders could not be adjusted, or a serum Ca x Phos product was > 70, the dosage of Hectorol was reduced to a rate of one level below the previous dose.

Patient Population: Patients qualified for inclusion in this study if they completed study H-108 (oral Hectorol) and were evaluable for statistical purposes. Subjects who discontinued prematurely from study H-108 after Week 16 because of concomitant use of calcitriol were allowed to participate in this study if they met the other eligibility criteria.

Inclusion criteria included:

- Aged 20 to 75 years
- Had been on hemodialysis for at least 4 months
- Had an average serum Phos in the range of 2.5 to ≤ 6.9 mg/dl during the 2 months prior to enrolling in study H-108
- Had a history of elevated iPTH (> 400 pg/ml) when not receiving vitamin D therapy
- Had a normal or minimally reduced average serum albumin during the previous two months (not lower than 0.5 g/dL below the normal range)

Exclusion criteria included:

- Having undergone partial or total parathyroidectomy after completing H-108
- Having a serum aluminum level of > 40 ng/ml

The following patients were precluded from entering the 8-week treatment period

- Subjects who failed to exhibit an average serum phosphorus in the range of 2.5 to $\leq$ 6.9 mg/dl during the washout period
- Subjects who failed to exhibit an average serum calcium of $\leq$ 10.5 mg/dl during the washout period
- Subjects who failed to have an average Ca x Phos product of $\leq$ 70 during the washout period
- Subjects who switched to ambulatory peritoneal dialysis
- Subjects who did not have at least one iPTH value above 400 pg/ml during the first 7 weeks of the washout period

Endpoints: The primary efficacy endpoint was the level of serum iPTH. Serum iPTH levels were measured weekly using a [redacted] The primary safety endpoints were the levels of serum Ca and Phos. These parameters were also measured weekly. Routine chemistries were measured every 4 weeks.

Statistical Analyses: The sponsor defined evaluable subjects as follows: the subject maintained an average serum Phos in the range of 2.5 to $\leq$ 6.9 mg/dl during the treatment period; the subject received at least 80% of the test drug; the subject did not receive calcitriol or aluminum-containing products during the study; and analysis of the subject's plasma confirmed a circulating level of 1-alpha, 25-$(OH)_2D_3$ that was consistent with the prescribed dosage of test drug.

Baseline values for serum Ca, Phos, and iPTH were defined as the average of the data collected during the last three visits during the washout period. The sponsor defines two Intent-to-Treat analyses: 1) all subjects who received test medication, and 2) all subjects enrolled whether or not they received test medication. Per protocol analyses included data on those subjects who completed the study and were evaluable for statistical purposes.

The significance of the change in the efficacy and safety parameters from baseline to Endpoint was determined using a paired t-test. Paired t-tests were also used to compare, at comparable times points, the mean value of the efficacy and safety parameters in H-108 and H-114.

Results

Patient Disposition: A total of 46 subjects were eligible for enrollment into the washout phase. Forty subjects agreed to participate in this study and were enrolled into the washout phase. Twenty-eight of these participants completed the washout phase and were admitted into the open label treatment phase. Most of the subjects who did not enter the open label phase were deemed ineligible because of inappropriately low iPTH levels during the washout phase. Of the 28 patients who started 24 were considered evaluable at the end of the study. Two subjects were discontinued: one for switching to two times per week dialysis, and the other for low compliance due to a problem with graft difficulties. The other two subjects were deemed non-evaluable because of a high Phos level and low compliance due to hospitalization. These four subjects are included in the ITT analyses.

Protocol Violations: Most of the protocol violations were isolated cases of inappropriate drug dosing or missed blood draws.

Patient Demographics: In addition to the demographic characteristics for the subjects enrolled into the open-label phase of this study, the following table provides the patient demographic profiles for the subjects enrolled into the open-label phase of study H-108.

Demographic Characteristic	H-108 (n=62)	H-114 (n=28)
Mean Age (range) (yrs)	(22-75)	54 (23-73)
% Male	55%	50%
% Black	58%	61%
% Caucasian	31%	25%
Serum iPTH (pg/ml)	822.9	697.6
Serum Ca (mg/dl)	9.00	9.05

Demographic Characteristic	H-108 (n=62)	H-114 (n=28)
Serum Phos (mg/dl)	5.05	4.69
Mean # Months on Dialysis	52.9	65

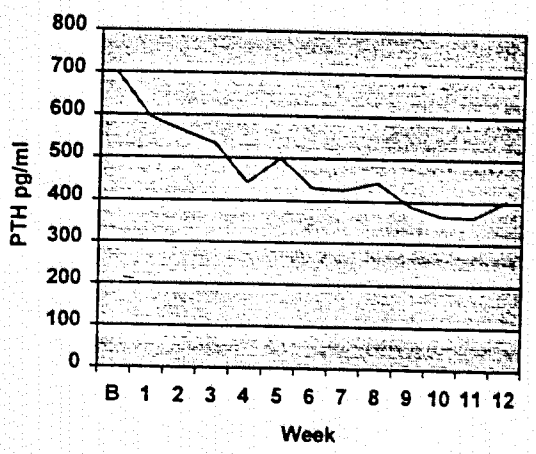
Mean Weekly Drug Dosage and Compliance: The mean weekly drug dosage ranged from 8.88 ug to 12.13 ug. As expected in a trial where study drug is administered at dialysis sessions, compliance was very high: on average 96%.

Primary Efficacy Outcome

Serum iPTH Levels (per protocol)

The mean serum iPTH level at baseline was 705 pg/ml (range [redacted] pg/ml). At Week 12, the mean iPTH level was reduced to 405 pg/ml ($p<0.001$). Results from the ITT analysis were similar. As observed in H-114-Memphis, mean weekly levels of iPTH decreased gradually during the study. Levels appeared to be continuing to decrease at Week 12.

Mean Weekly PTH Levels



Compared to baseline, the mean values for iPTH during Weeks 1-12 were statistically significantly lower ($p \leq 0.004$).

One hundred percent of the subjects achieved a iPTH suppression of $\geq$ 30% on or before Week 8. The average dose of IV Hectorol required to achieve $\geq$ 30% iPTH suppression was 3.8 ug per dialysis session.

Seventy-five percent of the subjects reached the pre-determined targeted iPTH range of 150 – 300 pg/ml one at least one occasion during the study. Twelve of 28 patients had iPTH levels below 300 pg/ml on greater than 3 consecutive occasions.

Primary Safety Outcomes

Serum Calcium Levels (per protocol)

The mean serum Ca level at baseline was 9.1 mg/dl. At Week 12 the mean Ca level had increased to 9.9 mg/dl ($p<0.001$). Results from the ITT analysis were similar. This increase of 0.8 mg/dl was similar to that observed during 12 weeks of therapy with oral Hectorol in study H-108. Importantly, the mean level of serum albumin did not change significantly from baseline to Week 12. The maximum serum Ca level recorded during the study was 13.4 mg/dl.

Episodes of Hypercalcemia

Hypercalcemia was defined as a level > 11.2 mg/dl. There were 3 episodes of hypercalcemia in 3 subjects during the 12-week study period (0.9 episode/100 patient weeks). This incidence of 0.9 episodes/100 patient weeks during treatment with IV Hectorol compares to 3.9 episodes/100 patient weeks with oral Hectorol.

Serum Phosphorus Levels (per protocol)

The mean serum Phos level at baseline was 4.5 mg/dl. At Week 12 the mean Phos level was still 4.5 mg/dl ($P<0.001$). Results from the ITT analysis were similar. For comparison, during the open label portion of the oral Hectorol study the mean Phos level increased from 4.8 mg/dl at baseline to 5.5 mg/dl. The maximum serum Phos level recorded during the study was 10.3 mg/dl.

Episodes of Hyperphosphatemia

Hyperphosphatemia was defined a level > 8.0 mg/dl. There were 8 episodes in 4 patients during the 12-week study period (3.7 episodes/100 patient weeks). This incidence of 2.4 episodes/100 patient weeks during treatment with IV Hectorol was the same as that observed with oral Hectorol.

1alpha ,25-$(OH)_2D_2$ Levels

Predialysis levels of 1alpha, 25-$(OH)_2D_2$ were below the limit of detection [redacted] in most of the subjects at baseline. The average level of 1alpha, 25-$(OH)_2D_2$ (the active metabolite of Hectorol) at baseline was 5.2 pg/ml. At Week 12 the mean level had increased to 22.5 pg/ml ($p<0.001$). For comparison, in H-108-LA, the mean level of 1alpha, 25-$(OH)_2D_2$ increased from 5.1 pg/ml at baseline to 28.8 pg/ml at Week 12.

Serious Adverse Events

No patient died during treatment with IV Hectorol. Eight subjects experienced one or more serious adverse events during treatment with IV Hectorol. Three subjects had occlusions of their grafts that required short hospital stays. Two subjects were hospitalized for cardiac evaluations due to complaints of chest pain and DOE. Two participants underwent orthopedic procedures: one for avascular necrosis of the ankle and the other for repair of a nonhealing fracture of the left ankle. The eighth patient was hospitalized 3 times for Staph septicemia from an AV graft.

Sponsor's Conclusions

This study demonstrates that 1 alpha-OH-D_2, when given intravenously, three times a week, is efficacious and safe in lowering plasma levels of iPTH in patients with moderate-to-severe-secondary hyperparathyroidism associated with ESRD. The results of this protocol as compared with Protocol No. H-108 support the conclusion that intravenous 1 alpha-OH-D_2 is similar in efficacy and safety to the oral formulation of 1 alpha-OH-D_2. Both formulations have demonstrated they are an efficacious and safe alternative to calcitriol in uremic subjects with secondary hyperparathyroidism.

Medical Officer's Discussion

In May of 1999, Dr. Lutwak, primary medical reviewer, recommended approval of oral Hectorol for the indication of lowering iPTH levels in ESRD patients on hemodialysis. This recommendation was based primarily on data from clinical study H-108 (conducted at multiple sites in the Los Angeles and Memphis areas).

In support of approval of the IV formulation of Hectorol, Bone Care International submitted data from a pharmacokinetic study (H-103) and from a crossover extension study of H-108 (H-114). The Biopharmaceutical reviewers, Drs. Kavanagh (oral Hectorol) and Shore (IV Hectorol) did not feel that adequate pharmacokinetic information was provided by the company. The two main deficiencies were:

Given the stated limitations of the pharmacokinetic data, assessment of the efficacy (and safety) of IV Hectorol is based on pharmacodynamic data from study H-114. At the Division's suggestion, study H-114 was conducted as a crossover extension from study H-108 (oral formulation).

As with any crossover study in which all subjects receive the same treatment in the first phase, the primary concern regarding the evaluation of IV Hectorol's efficacy (lowering of iPTH) relates to enrichment, or the possibility that subjects who completed the oral Hectorol study (H-108) and crossed over into the IV study had a different (or more favorable) response to Hectorol than those subjects who discontinued from study H-108 and did not enter H-114. In an analysis comparing the 70 evaluable patients who completed H-108 and entered H-114 with the 33 evaluable patients who prematurely discontinued treatment during H-108, there was no evidence that the mean percent changes in plasma iPTH differed in a meaningful way between these two groups of subjects (see Table in Appendix).

The primary concern regarding the evaluation of IV Hectorol's safety (hypercalcemia and hyperphosphatemia) also relates to enrichment, or in this case, the possibility that subjects who completed the oral Hectorol study (H-108) and crossed over into the IV study had a lower risk for hypercalcemia and/or hyperphosphatemia compared with subjects who discontinued from study H-108 and did not enter H-114. The rates of hypercalcemia were 3.2/100 Rx-weeks and 1.5/100 Rx-weeks in the subjects who completed vs. those who did not complete H-108, respectively. The rates of hyperphosphatemia were 4.3/100 Rx-weeks and 4.7/100 Rx-weeks in the subjects who completed vs. those who did not complete H-108, respectively. Further, an additional safety parameter, over suppression of iPTH (levels < 150 pg/ml), occurred at a higher rate in completers vs. non-completers (8.0/100 Rx-weeks vs. 5.5/100 Rx-weeks). These data do not support the idea that subjects who completed H-108 had a more favorable safety profile when compared to non-completers.

Similar to treatment with oral Hectorol, treatment with IV Hectorol decreased levels of serum iPTH steadily throughout 12 weeks of dosing. Compared to baseline, the mean percent reductions in iPTH were statistically significantly greater during all weeks of treatment. Furthermore, the response to IV Hectorol was comparable (clinically and statistically) to that seen with oral Hectorol (see figures 1 and 2 in Appendix).

It merits mention that treatment with oral Hectorol may be associated with a greater risk for hypercalcemia and hyperphosphatemia than treatment with IV Hectorol. Despite comparable reductions in iPTH levels, there was a greater incidence of both hypercalcemia and hyperphosphatemia when subjects were treated with oral Hectorol (mean doses of 20 to 28 ug per week) than when these subjects were treated with IV Hectorol (mean doses of 9 to 11 ug per week).

One explanation for this observation is the possibility that intestinal mucosal cells activate oral Hectorol (a prodrug) to the active metabolite, 1-alpha, 25-dihydroxyvitamin D_2[1] (this would not occur to the same degree following IV drug administration). If this observed difference in risk for hypercalcemia and hyperphosphatemia between the oral and IV formulations of Hectorol is a physiologically based finding, the IV formulation might prove to be safer and therefore more efficacious than the oral formulation (hypercalcemia often limits increasing vitamin D dosage).

In conclusion, the oral formulation of Hectorol was deemed safe and effective for marketing in 1999. Due in part to the lack of an assay to measure the parent drug, data from a pharmacokinetic study comparing drug levels following oral and IV administration was not considered appropriate or adequate. At the division's suggestion, the sponsor conducted a pharmacodynamic crossover study comparing serum iPTH levels following oral and IV drug administration. The data submitted support the relative (compared with the oral formulation) efficacy of IV Hectorol in the management of secondary hyperparathyroidism. Given that the risk for hypercalcemia and hyperphosphatemia was lower when patients received IV Hectorol compared with oral Hectorol, it is possible that the IV formulation is in fact the "safer" and preferred formulation.

[1] Jones G, Byford V, Guo Y, et al. Cultured human keratinocytes both activate and catabolize 1alpha-hydroxyvitamin D2 analogs. J Bone Mineral Res 1999; 14:S305.

Regulatory Recommendation

For the reasons discussed above, I recommend that the IV formulation of Hectorol be approved for the management of secondary hyperparathyroidism [redacted]

/S/ 3/22/07
Eric Colman, MD

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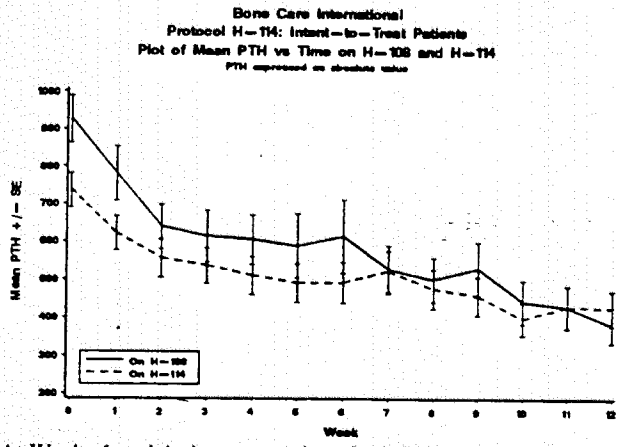
Appendix

Table Comparison of serum iPTH levels in subjects who completed H-108 and entered H-114 with subjects who completed H-108 but did not enter H-114.

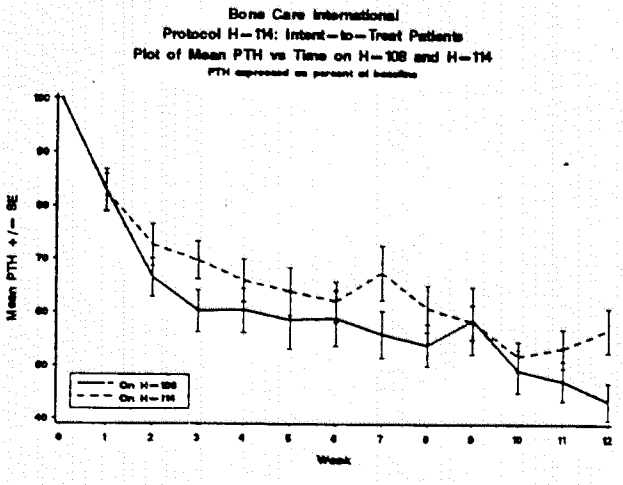
	Mean Weekly % Change from Baseline in iPTH											
Group	1	2	3	4	5	6	7	8	9	10	11	12
Entered 114 (n=70)	-17	-34	-40	-40	-42	-42	-42	-43	-42	-52	-53	-56
Did Not Enter 114 (n=33)	-23	-35	-37	-41	-46	-49	-47	-50	-43	-46	-54	-52

Figure 1 (Mean Weekly Serum iPTH levels in Subjects Who Participated in H-108 and H-114)



At Weeks 1 and 4, the mean values for iPTH were statistically significantly lower ($p<0.05$) for subjects in H-114 vs. the value for subjects in H-108

Figure 2 (Mean Weekly Serum iPTH levels in Subjects Who Participated in H-108 and H-114)



At Week 12, the mean iPTH value for subjects in H-114 was statistically significantly greater ($p<0.05$) vs. the mean value for subjects in H-108.

MEDICAL OFFICER'S RE-REVIEW OF RESUBMISSION OF NDA

NDA No. 21-027, Vol. 5.1
DRUG: HECTOROL INJECTION
doxercalciferol
SPONSOR: Bone Care International
One Science Court
Madison, WI 53711
ATTN: Darlene M. Kyllo
Tel: 608-236-2500

DATE OF SUBMISSION: Jan. 31. 1999
DATE RESUBMITTED: Dec. 20, 1999
DATE OF REVIEW: Jan. 20, 2000
DATE THIS REVIEW: March 2, 2000

INDICATION: Treatment of secondary hyperparathyroidism associated with end-stage renal disease

RELATED NDA: No. 20-862

No new clinical data are submitted. The present submission consists of re-analysis of the pharmacodynamic data in the original submission of Jan. 31, 1999.

Since the Sponsor has submitted a revised label for this product and since other review disciplines continue to evaluate the submission, I have revisited this submission to examine the clinical aspects of the application.

The data submitted in support of the present NDA are from an open-label protocol carried out at two sites. The subjects participating were those who had completed a previous protocol studying orally administered doxercalciferol who had been invited to enter the new study. Prior to receiving the test drug, the patients underwent a "washout" phase to eliminate the effects of other vitamin D active substances. This "washout" phase has been used as the "control" phase for the present NDA.

Table 1 is a "tree" showing the attrition process from the initial randomization of 211 subjects enrolled in the original study of oral doxercalciferol to the 64 subjects considered evaluable for the present study of i.v. doxercalciferol.

As may be noted from reported numbers of subjects in the U.S. target population (**Table 2**), the subjects studied for this Application are a small sample of those for whom this drug may be prescribed. Thus evaluation of potential selection bias becomes critical. The subjects studied were 100% black in one study and 61% black. As shown in **Table 3**, ESRD patients are primarily White (almost 2:1).

The indication for the drug is reduction of serum iPTH levels to the range of 150-300 picograms/ml. Serum iPTH was within the targeted range on 3 or more measurements in 16/28 subjects at one center and in 25/42 at the other. Serum iPTH levels after the "washout" phase ranged between [redacted] The mean values for serum iPTH after the washout had standard errors between 9 and 17%. In the absence of concurrent controls, I cannot rule out the possibility that the observed changes of possibly meaningful clinical significance (seen in 41/60 subjects) may have been due to the natural history of the disease or to other influences.

Although this was not a defined end-point, it is instructive examine the point value of the last measurement of iPTH after 12 weeks of treatment of these 64 subjects for both efficacy and safety considerations (**Table 4**). Values >300 picograms/ml were seen in

48% of the completers (suggesting lack of efficacy) and values below 150 picograms/ml occurred in 20% (suggesting safety concerns such as frozen bone). **Thus, this agent may be effective in 32% of the trial subjects.**

Criteria for studies for approval of an NDA are discussed in the Code of Federal Regulations in the section quoted below.

***FROM* 21 CFR Chapter I, Subchapter D §314.126 Adequate and well-controlled studies**

(a) The purpose of conducting clinical investigations of a drug is to distinguish the effects of the drug from other influences, such as spontaneous change in the course of the disease, placebo effect, or biased observation.

(b) An adequate and well-controlled study has the following characteristics:

(2) The study uses a design that permits a valid comparison with a control to provide a quantitative assessment of drug effect.

(i) Placebo concurrent control.
(ii) Dose-comparison concurrent control.
(iii) No treatment concurrent control.
(iv) Active treatment concurrent control.
(v) Historical control. ...Because in historical controls populations usually cannot be assessed with respect to pertinent variables as can concurrent control populations, historical control designs are usually reserved for special circumstances. Examples include studies of disease with high and predictable mortality (for example, certain malignancies) and studies in which the effect of the drug is self-evident (general anesthetics, drug metabolism).

(e) Uncontrolled studies or partially controlled studies are not acceptable as the sole basis for the approval of claims of effectiveness.

The subjects studied in this Protocol were not representative of the target population in respect to race or gender. They were not a randomized sampling since 14% of the originally enrolled population had been disqualified or discontinued because of hyperphosphatemia occurring at some phase of the trial of the related oral form of the drug. The "control" phase of the submitted study was the period prior to use of drug (during which prior drug effects were being washed out). This is a form of historical control which makes distinguishing the effect of drug from other influences extremely difficult. This drug does not qualify as a case of "special circumstances."

As stated above [1 CFR Chapter I, Subchapter D, §314.126, (e)], ...partially controlled studies are not acceptable as the sole basis for the approval of claims of effectiveness.

MEDICAL OFFICER'S CONCLUSION AND RECOMMENDATIONS

Based on the considerations discussed above, it is my opinion that this NDA is **Not Approvable,**

/S/

/Leo Lutwak, M.D., Ph.D., FACP
Medical Officer
March 8, 2000
Recalculated March 30, 2000

/S/ 4/3/00

CC: NDA Archive
HFD-510/HedinR/ColmanE/LutwakL/SchneiderB/ZilbersteinM
HFD-715/SahlrootT
HFD-870/ShoreR

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TABLE 1

FLOW CHART OF SUBJECT PARTICIPATION
(*Submission Appendix 11*)

Enrolled Subjects (Randomized) Study H-108, NDA 20-862
N = 211
Discontinued or Disqualified:73 (11 because of high phosphate or CaXP)

Subjects Beginning Open Label, NDA 20-862
N = 138 (65% of randomized)
Discontinued because of high phosphate: 1

Subjects Beginning Blinded Treatment, NDA [redacted]
N = 122 (58% of randomized)
Discontinued because of high phosphate: 1

Completing Subjects, NDA 20-862
N = 110 (52% of randomized)
Disqualified because of high phosphate: 9

Evaluable Subjects, NDA 20-862
N = 99 (47% of randomized)
Disqualified or discontinued because of high phosphate, entire study: 21

Eligible Subjects (from last group above) for NDA 21-027, Study H=114
N = 107 (50.8% of randomized, originally)

Enrolled, NDA 21-027
N = 97 (46% of randomized originally; 90.4% of eligible)
Disqualified or Discontinued because of high phosphate: 4

Subjects Beginning Open-Label Treatment, NDA 21-027
N = 70 (33.2% of randomized; 65.5% of eligible)
Discontinued because of high phosphate: 0

Subjects Completing Treatment, NDA 21-027
N = 68 (32.3% of randomized; 63.8% of eligible)
Disqualified because of high phosphate: 4

Evaluable Subjects, NDA 21-027
N = 64 (30.3% of randomized; 60% of eligible)
Disqualified or discontinued because of high phosphate, NDA 21-027: 8

Disqualified or discontinued because of high phosphate, from initial enrollment NDA 20-862 : 29 (13.7%)

TABLE 2

LIVING ESRD PATIENTS, DECEMBER 1997
(from USRDS Database derived from HCFA REBUS, 1998)

Total: 307,987
All Dialysis: 221,596
Center Hemodialysis: 191,494

TABLE 3
PREVALENCE COUNTS, DECEMBER 1997
(from USRDS Database derived from HCFA REBUS, 1998)
RACE: White, 186341/304083 (61.3%)
Black, 97503/304083 (32.1%)
GENDER: Male , 54.3%; Female, 45.7%

TABLE 4
SERUM iPTH

Study Phase*	Week 0			Week 12		
	<150	150-300	>300	<150	150-300	>300
Oral	0 (0%)	2 (2.3%)	67 (97.1%)	14 (20.3%)	29 (42.0%)	26 (37.7%)
I.V.	1 (1.4%)	3 (4.3%)	65 (94.2%)	14 (20.3%)	22 (32.9%)	33 (47.8%)

* The iPTH values are for the 69 subjects who participated in both H-108 (the study of oral Hectorol) and in H-114 (the study of i.v. Hectorol).

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ON ORIGINAL

MEDICAL OFFICER'S REVIEW OF NDA SAFETY UPDATE

NDA No. 21-027
DRUG: **HECTOROL INJECTION**
doxercalciferol
SPONSOR: Bone Care International
One Science Court
Madison, WI 53711
ATTN: Darlene M. Kyllo
Tel: 608-236-2500

DATE OF SUBMISSION: March 20, 2000
DATE REC'D, CDER: March 23, 2000
DATE REC'D, M.O.: March 23, 2000
DATE REVIEWED: April 3, 2000

INDICATION: Treatment of secondary hyperparathyroidism associated with end-stage renal disease (ESRD).

The submission covers the period from the cut-off of the NDA data (February 11, 1998) through March 1, 2000. The only clinical study conducted in that period was No. H-120, a multi-center, open-label, parallel group study to compare doxercalciferol to calcitriol in ESRD patients. The study was discontinued prematurely because of poor patient recruitment and enrollment. Of the 20 subjects enrolled, 6 subjects were randomized, 4 to Hectorol and 2 to Calcijex. No information is provided for the 14 subjects not randomized, nor for the 2 subjects on Calcijex.

All four subjects on Hectorol were black, 3 males and 1 female. The age range was 37 to 62. Mean duration of treatment was 13.5 weeks (actual values not given). The only adverse event reported is the development of elevated Ca X P product in one patient.

MEDICAL OFFICER'S COMMENTS

No conclusions are possible from this short, small, incomplete study.

/S/

Léo Lutwak, M.D., Ph.D., FACP
Medical Officer
April 3, 2000

/S/ 4/3/00

CC: NDA Archives
HFD-510/HedinR/ColmanE/LutwakL

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