After the baseline period, up to 10 patients who met the inclusion/exclusion criteria were randomized to receive active drug or placebo. Each patient received 3 injections of active drug or placebo at 48 to 72-hour intervals (at the end of their regular hemodialysis session) every week for4 weeks (a total of 12 doses). Each subsequent group started study drug treatment only after the previous group of patients had successfully completed two weeks of treatment and none of the following endpoints had been achieved: 75% of the patients in the preceding group had a 30 percent or greater decrease from the maximal baseline serum iPTH level 50% or more of the patients in the preceding group developed hypercalcemia (serum Ca greater than 11.5 mg/dL) 50%or more of the patients in the preceding group developed elevated Ca x P product (> 70). If any safety concerns arose in the preceding groups, further patients were entered into the treatment phase of the study only at the concurrence of the Abbott Monitor and the Investigator. Blood samples were drawn to assess the pharmacokinetic profile of Paracalcin Injection immediately prior to dosing and at designated post-injection times, at the first and last dose.

Demographics and Patient Population

Seventy-one patients were enrolled into the study. Thirty-five patients entered into the treatment phase of the study. Of those patients, 22 received active drug and 13 received placebo. Males accounted for 51% (18/35) and females accounted for 49% (17/35) of the treated patients. Eighty-six % (30/35) of the treated patients were Black, 11% (4/35) were Hispanic, and three % (1/35) were Caucasian. The mean age of treated patients was 50 years, with a standard deviation of 16 years and a range of 18 to 84 years. The gender frequencies, mean age, and mean weight were comparable between the two treatment groups.

Results

Of the 35 patients treated in the four dosing groups, 22 patients received Paracalcin Injection and 13 patients received placebo. Fifteen of the 22 patients receiving Paracalcin Injection achieved the 30% iPTH reduction endpoint. Only one patient experienced elevated Ca (> 11.5 mg/dL) which was observed prior to or coincident with the achievement of the iPTH endpoint (patient showed a 48% iPTH reduction). Calcium remained normal at all instances of elevated Ca x P product prior to or coincident with the achievement of the iPTH endpoint.

Patients Results and Study Endpoints

Study Drug	**Dose (mg/kg)**	**Patients achieving 30% reduction in iPTH**	**Patients with elevated calcium before, at, and after iPTH endpoint**			**Patients with elevated Ca x P before, at, and after iPTH endpoint**		
			before	at	after	before	at	after
placebo	–	2/13	0	0	0	1	0	0
active	0.04	4/6	0	0	0	0	0	0
active	0.08	¼	0	0	0	0	0	0
active	0.16	5/6	0	1*	2	1	1	3
active	0.24	5/6	0	0	1	2	0	0

Group 5 did not enter the treatment phase of the study because Group 3 met the study design endpoint criteria. Group 4 had begun the treatment phase by that point and was allowed to complete the study. Six serious adverse experiences were reported; though none were associated with administration of study drug.

A total of 89 adverse experiences were recorded during the study. Overall, 77% of placebo-treated patients (10/13) and 77% of active-drug patients (17/22) reported at least one adverse experience. For all

adverse experiences, 66 of 89 (74%) were rated as mild in intensity, 21 of 89 (24%) were rated as moderate in intensity, and 2 of 89 (2%) were rated as severe in intensity. No statistically significant difference in incidence rate per patient was shown between treatment groups for the total, individual Body System, or COSTART terms.

Conclusion: Paracalcin Injection safely reduced serum iPTH in doses ranging from 0.04 to 0.24 mcg/kg. Eighty-three % (5/6) of the patients in each of the 0.16 mcg/kg and 0.24 mcg/kg dosages groups achieved the 30% reduction endpoint in iPTH. At the two highest doses, elevated calcium was observed coincident with or after achievement of the iPTH reduction endpoint in 60% (3/5) of the 0.16 mcg/kg dosage group and 20% (1/5) of the 0.24 mcg/kg dosage group. Elevated Ca x P occurred prior to the achievement of the iPTH endpoint in 20% (1/5) of the 0.16 mcg/kg dosage group and 40% (2/5) of the 0.24 mcg/kg dosage group. Coincident with or after achievement of the iPTH reduction endpoint, 80% (4/5) of the 0.16 mcg/kg dosage group and 0% (0/5) of the 0.24 mcg/kg dosage group showed increased Ca x P product. Overall, two instances of elevated Ca x P product occurred in placebo patients, with one of these placebo patients achieving the iPTH endpoint. At all instances of elevated Ca x P product up to and including achievement of iPTH reduction endpoint Ca remained normal.

7.4 Safety Summary—General Safety Conclusions

Safety data derived from eight clinical studies, completed and ongoing, were evaluated for safety in this NDA. Phase III placebo-concurrent controlled studies 95035, 95036, and 95037, and the Phase II study, 95022 have been completed. Interim safety data are included from studies 95028 and 95034 (comparison with calcitriol studies), 95029 (rollover study for patients from other studies), and 96004 (long-term study) and includes all patients who could have received Paracalcin Injection as of October 1997.

The safety data are presented according to three categories of studies: Phase III placebo-concurrent controlled studies, Phase II/III placebo-concurrent controlled studies, and finally, all Phase II/III studies which encompass the Phase II/III placebo-concurrent controlled studies plus 95028, 95029, 95034, and 96004.

There were three Phase I studies. Twenty-five subjects received paracalcin doses ranging _____ apart for three IV doses. These are described in Study Reports 95003, 95018, and 96016. The first two studies were placebo-concurrent controlled. No clinically significant adverse experiences were noted. A decision was made not to combine the subjects from those studies with the patient population (chronic renal disease with hyperparathyroidism) in the Phase II/III studies. It was considered that the differences in the populations would distract rather than enhance the understanding of the integrated results.

Statistical Conventions

Adverse Events

Safety analyses were performed on all treated patients. This includes all patients that were randomized and received at least one dose of study drug.

For adverse events, a patient who reported the same COSTART term more than once was counted only once for that COSTART term and categorized by the most intense occurrence. A patient who reported more than one adverse experience was counted only once for each applicable body system and once for Overall and categorized by the most intense adverse experience.

Clinical Laboratory Data

Laboratory parameters for chemistry and hematology were analyzed using a one way analysis of variance (ANOVA) and Fisher's Exact test. Laboratory parameter data was collected at enrollment, final baseline, at various times during the studies, and at final evaluation for each patient.

Statistical and Analytical Plans

Descriptive statistics such as frequency, means, standard error of the mean, minimum, and maximum values were calculated for all treated patients, and by time for all primary variables of interest.

8 EFFICACY SUMMARY

9 LABELING REVIEW

MEDICAL OFFICER'S REVIEW OF LABEL

DATE OF REVIEW: March 12, 1998; Revised March 19, 1998

The following is the submitted label with my comments and revisions inserted in italics.

[TRADE NAME]™

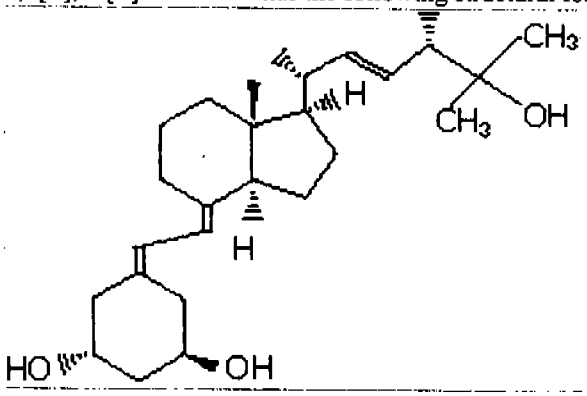
Comment: *The proposed name is not acceptable; it is too similar to "capoten" and "Captopril" both of which are drugs that may be prescribed for patients similar to the target population for this drug.*

Paracalcin Injection
Ampul
Fliptop Vial

DESCRIPTION

[TRADE NAME]™ (Paracalcin Injection) is synthetically manufactured and is available as a sterile, clear, colorless, aqueous solution for intravenous injection. Each mL contains paracalcin, 5 mcg; propylene glycol, 30% (v/v); and alcohol, 20% (v/v).

Paracalcin is a white powder which is chemically designated as 19-nor-1α,3ß,25-trihydroxy-9,10-secoergosta-5,7[E],22[E]-triene and has the following structural formula:



Molecular formula is $C_{27}H_{44}O_3$.
Molecular weight is 416.65.

CLINICAL PHARMACOLOGY

In healthy subjects *[give number]*, plasma radioactivity after a single 0.16 mcg/kg intravenous bolus dose of ^{3}H-paracalcin (n=4) was attributed to parent drug. Paracalcin was eliminated primarily by hepatobiliary excretion, as 74% of the radioactive dose was recovered in feces and only 16% was found in urine. Several metabolites were detected in both the urine and feces, with no detectable unchanged paracalcin in the urine. *[These metabolites have not been identified nor is it known whether or not they are active.]* Together, these metabolites contributed 51% of the urinary radioactivity and 59% of the fecal radioactivity. In vitro plasma protein binding of paracalcin was extensive (>99.9%) and nonsaturable over the concentration range of 1 to 100 ng/mL.

Paracalcin Pharmacokinetic Characteristics in CRF Patients (0.24 mcg/kg dose)

Parameter	n	Values (Mean ± SD)
C_{max}	6	1850 ± 664 (pg/mL)
$AUC_{0-\_}$	5	27382 ± 8230 (pg•hr/mL)
CL	5	0.72 ± 0.24 (L/hr)
V_{ss}	5	6 ± 2 (L)
$t_{1/2}$†	32	14.3 ± 6.0 (hr)
RBC/Plasma Ratio‡		≥ <-0.04

† Harmonic mean and pseudo standard deviation based on the data from four studies and different dosages.
‡ Means of in vitro results in healthy subjects over a concentration range of 0.01 to 10 ng/mL.

Special Populations:

Paracalcin pharmacokinetics have not been investigated in special populations (geriatric, pediatric, hepatic insufficiency), or for drug-drug interactions. Pharmacokinetics were not race or gender-dependent. *[Was there adequate representation of races to warrant this statement?]*

INDICATIONS AND USAGE

[TRADE NAME] is indicated for the prevention and treatment of _____secondary hyperparathyroidism encountered with chronic renal failure. Studies in patients with chronic renal failure show that [TRADE NAME] suppresses PTH levels _____

Comments: *1) The indication for prevention and treatment of renal osteodystrophy is not supported by the data submitted. There are no studies of bone presented. The assumption that prevention of elevation of iPTH will lead invariably to prevention of bone disease must be supported by data such as bone biopsy, skeletal x-rays, measurements of bone mineral density, biochemical indices of bone turnover - preferably a combination of several of these.*

2) Data supporting the claim for suppression of PTH levels must be supported by data somewhere in the label, such as under Clinical Pharmacology.

3) The claim that paracalcin is superior to calcitriol is based on marginal differences as presented in the NDA. The claim may be made (if appropriate data are presented in the label) that paracalcin is at least as safe as calcitriol and, although not statistically significant, may carry lower risks of hypercalcemia.

CONTRAINDICATIONS

[TRADE NAME] should not be given to patients with evidence of vitamin D toxicity *[describe the evidence for toxicity that should be avoided.]* or hypersensitivity to any ingredient in this product (See PRECAUTIONS, General).

WARNINGS

[Supplements] of vitamin D and its derivatives (>400 IU/d) should be withheld during treatment with [TRADE NAME]. Like other forms of vitamin D, overdose of [TRADE NAME] may require emergency attention. Chronically elevated calcium levels can lead to metastatic calcification. The serum calcium times phosphorus (Ca x P) product should not be allowed to exceed *70]*. Radiographic evaluation of suspect anatomical regions may be useful in the early detection of this condition.

Comment: *The term "medicinal" is archaic and vague; examples of the forms of vitamin D should be given.*

The NDA used "70" as the cutoff point for Ca x P.

PRECAUTIONS

1. **General:** administration of [TRADE NAME] may place patients at risk of hypercalcemia and elevated Ca x P products. Therefore, during dose adjustment, serum calcium and phosphorus levels should be monitored closely *[twice weekly]*. If clinically significant hypercalcemia develops, the dose should be reduced or interrupted. Digitalis toxicity is potentiated by hypercalcemia of any cause, so caution should be applied when digitalis compounds are prescribed concomitantly with [TRADE NAME].
2. **Information for the Patient:** The patient should be instructed that to ensure effectiveness of [TRADE NAME] therapy, patients should adhere to their prescribed dietary regimen for calcium supplementation and phosphorus restriction. Appropriate types of phosphate-binding compounds may be needed to control serum phosphorus levels in patients with CRF (*Chronic Renal Failure)*. Patients should also be carefully informed about the symptoms of elevated calcium.

   Comment: *In the "Inclusion and Exclusion Criteria" for the pivotal studies, it was stated that the subjects "cannot require the chronic use of aluminum containing compounds for phosphate binding. The label should indicate this, probably under* ***PRECAUTIONS.***

3. **Essential Laboratory Tests:** Serum calcium and phosphorus should be measured at least monthly. Serum or plasma PTH is recommended to be measured every 3 months. An intact PTH (iPTH) assay is recommended for reliable detection of biologically active PTH in patients with CRF. During dose adjustment of [TRADE NAME], laboratory tests may be required more frequently.
4. **Drug Interactions:** specific interaction studies were not performed,

   -[Add sentence about digitalis here as well.]
5. **Carcinogenesis, Mutagenesis, Impairment of Fertility:** Long-term studies in animals to evaluate the carcinogenic potential of paracalcin have not been completed. Paracalcin was not genotoxic in the in vitro microbial mutagenesis assay with and without metabolic activation, in an in vitro mammalian cell mutagenesis assay with and without metabolic activation, in an in vivo mouse micronucleus assay, and in an in vitro human lymphocyte cell chromosomal aberration assay with and without metabolic activation. [TRADE NAME] had no effect on fertility (male or female) in rats at intravenous doses up to 20 mcg/kg/dose (equivalent to 10 to 125 times the 0.04 to 0.24 mcg/kg human dose based on pharmacologic and pharmacokinetic studies).
6. **Use in Pregnancy:** *Pregnancy Category C.* Fertility, general reproduction, embryotoxicity, and peri- and postnatal toxicity studies were conducted in rats and rabbits. Paracalcin had no effect on fertility or early general reproduction indices in rats. Minimal decreases in offspring viability were observed in pregnant rats and rabbits

treated with paracalcin, but only at dosages which were maternally toxic. No other effects on offspring development were observed. Paracalcin was not teratogenic.

There are no studies in pregnant women. [TRADE NAME] should be used during pregnancy only if the benefit justifies the potential risk to the mother and fetus.

7. **Nursing Mothers:** It is not known whether paracalcin is excreted in human milk. [TRADE NAME] has not been studied in nursing mothers and should only be given if the benefits to the mother outweigh the potential risks to the infant.
8. **Pediatric Use:** Safety and efficacy of [TRADE NAME] in patients under the age of 18 years has not been established.
9. **Use in the Elderly:** Of the patients receiving [TRADE NAME] in the four, placebo-controlled, CRF studies, 19% were 65 years or over. In clinical studies, no overall differences in efficacy or safety were observed between these patients 65 years or older and younger patients.

   Comment: *The robustness of this comment should be placed in context by stating the number of subjects in these studies, i.e., **40**, receiving the drug.*

ADVERSE REACTIONS *[Add description of signs and symptoms of hypercalcemia here.]*

[TRADE NAME] has been evaluated for safety in clinical studies in more than 300 CRF patients. In four, placebo-controlled, double-blind, multicenter studies, discontinuation of therapy due to any adverse experience occurred in 6.5% of 62 patients treated with [TRADE NAME] up to 0.24 mcg/kg three times per week and 2.0% of 51 patients treated with placebo for one to three months. No statistically significant difference was shown between treatment groups in incidence rate for the total number of patients experiencing at least one adverse event. Adverse experiences with a frequency of five occurrences or more, regardless of causality, are presented in the following table:

APPEARS THIS WAY ON ORIGINAL

Adverse Experience Incidence Rates for All Treated Patients
All Placebo-Controlled Studies

Adverse Event (COSTART III Term)	[TRADE NAME](n=62) number of events, (%)	Placebo(n=51) number of events, (%)
Overall	44 (71.0)	40 (78.4)
Body as a Whole	27 (43.5)	26 (51.0)
Chest pain	1 (1.6)	6 (11.8)*
Headache	7 (11.3)	7 (13.7)
Pain	5 (8.1)	9 (17.6)
Cardiovascular System	14 (22.6)	14 (27.5)
Vascular disorder	6 (9.7)	4 (7.8)
Digestive System	14 (22.6)	10 (19.6)
Nausea	7 (11.3)	4 (7.8)

* Statistically significant between groups.

A patient who reported the same COSTART term more than once was counted only once for that COSTART term, using the most intense occurrence.

In addition, the following adverse events were reported in at least three [TRADE NAME]-treated patients in placebo-controlled studies and open-label studies; a causal relationship with [TRADE NAME] has not been established. All clinically significant abnormal laboratory values were to be reported as adverse events:

Body as a Whole: accidental injury, chills, fever, flu syndrome, sepsis, abdominal pain, injection site reaction, malaise.

Cardiovascular System: hypertension, hypotension.

Digestive System: gastrointestinal hemorrhage, vomiting, diarrhea, dyspepsia.

Metabolic and Nutritional Disorders: edema.

Musculoskeletal System: arthralgia.
Nervous System: dizziness.
Respiratory System: cough increased, pneumonia, dyspnea, pharyngitis.
Skin and Appendages: rash.
Special Senses: ear pain.

OVERDOSAGE

The early and late signs and symptoms of vitamin D intoxication are associated with elevated calcium. Administration of [TRADE NAME] to patients in excess of their requirements may cause elevated calcium levels and Ca x P products. Chronically elevated calcium levels can lead to metastatic calcification (see WARNINGS). High intake of calcium, phosphate, or vitamin D-related compounds concomitant with [TRADE NAME] administration may lead to similar abnormalities.

Treatment of patients with clinically significant hypercalcemia consists of reduction of dose or interruption of [TRADE NAME] therapy, and includes institution of a low calcium diet, withdrawal of calcium supplements, patient mobilization, attention to fluid and electrolyte imbalances, assessment of electrocardiographic abnormalities (critical in patients receiving digitalis), and hemodialysis or peritoneal dialysis against a calcium-free dialysate as warranted. Serum calcium levels should be monitored frequently until normocalcemia ensues.

DOSAGE AND ADMINISTRATION

The currently accepted target for iPTH levels in CRF patients _____ *[is]* from 1.5 to 3 times the non-uremic upper limit of normal.

_____ *[What is the basis for this recommendation? It does not appear in the NDA.]* is 0.04 mcg/kg to 0.24 mcg/kg administered as a bolus dose no more frequently than every other day.

If a satisfactory response is not observed, the dose may be increased by 0.04 mcg/kg/dose at 2 to 4 week intervals. During any dose adjustment period, serum calcium and phosphorus levels should be monitored more frequently, and if an elevated calcium level or a Ca x P product greater than *[70]* is noted, the drug should be immediately reduced or interrupted until these parameters are normalized. Then, [TRADE NAME] should be reinitiated at a lower dose. Doses may need to be decreased as the PTH levels decrease in response to therapy. Thus, incremental dosing must be individualized and commensurate with serum PTH, calcium and phosphorus levels.

The following table is a suggested approach in dose titration:

PTH Level	Suggested Dosing Guidelines [TRADE NAME] Dose
the same or increasing	increase
decreasing by <30%	increase
decreasing by >30%, <60%	maintain
decreasing by >60%	decrease
one and one-half to three times upper limit of normal	maintain

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Discard unused portion.

HOW SUPPLIED

[TRADE NAME] (Paracalcin Injection) 5 mcg/mL is supplied as a single dosage strength, in 1, 2, and 5 mL single patient use ampuls or Fliptop Vials.

List No.	Volume/container	Conc.	Total Content
1658	1 mL/Fliptop Vial	5 mcg/mL	5 mcg
1658	2 mL/Fliptop Vial	5 mcg/mL	10 mcg

1658	5 mL/Fliptop Vial	5 mcg/mL	25 mcg
3043	1 mL/ampul	5 mcg/mL	5 mcg
3043	2 mL/ampul	5 mcg/mL	10 mcg
3043	5 mL/ampul	5 mcg/mL	25 mcg

Store at controlled room temperature 15° to 30°C (59° to 86°F).
Caution: Federal (USA) law prohibits dispensing without prescription.

10 CONCLUSIONS

11 COMMENTS AND RECOMMENDATIONS

11.1 COMMENTS

11.1.1 Proposed Trade Name (*cf.* Section 1.2.2): The proposed name is not acceptable; it is too similar to "capoten" and "Captopril" both of which are drugs that may be prescribed for patients similar to the target population for this drug.

11.1.2 Proposed Indications (*cf.* Section 1.5): The indication for prevention and treatment of renal osteodystrophy is not supported by the data submitted. There are no studies of bone presented. The assumption that prevention of elevation of iPTH will lead invariably to prevention of bone disease must be supported by data such as bone biopsy, skeletal x-rays, measurements of bone mineral density, biochemical indices of bone turnover - preferably a combination of several of these.

11.1.3 Pharmacokinetics (*cf.* Sections 6.1.2, 6.1.3): Pharmacokinetic studies were conducted in normal subjects and in patients with no evidence of liver disease. Since hepatic dysfunction is common in patients with end stage renal disease, studies should be done in a population with expected abnormalities of liver function.

11.1.4 Pharmacodynamics (*cf.* Sections 6.3, 7.1.3): In a study of 4 normal subjects given isotopically labeled drug, metabolites were found in urine and in feces. These metabolites were not identified chemically nor in terms of biologic action. Since it is highly probable that the formation of metabolites may be affected qualitatively and quantitatively by renal disease and by hepatic disease, characterization of these substances chemically, metabolically, and physiologically, becomes essential for prediction of pharmacological function . The Sponsor notes that the pattern of metabolite distribution was similar in several animal models to that seen in humans and thus the questions could be answered, in part, by appropriate preclinical studies.

11.1.5 Comparison with Calcijex (*cf.* Section 7.3.1.2.5): The differences between paracalcin and Calcijex are not sufficiently robust to permit a claim of superiority.

11.2 THIS APPLICATION IS APPROVABLE. "APPROVAL" requires:

- acceptable Trade Name
- modification of Indication
- characterization of metabolites
- commitment to studies in pediatric population
- commitment to phase 4 studies
- modification of label

/S/

Leo Lutwak, M.D., Ph.D.
March 20, 1998

/S/ 4-6-98

Gloria Troendle, M.D.

/S/ 4-9-98

CC: NDA Archives
HFD-510 Archives
HFD-510/GTroendle/LLutwak/DColeman/SMarkofsky/DHedin
HFD-715/BElashoff
HFD-870/CJones

MEDICAL OFFICER MEMORANDUM
NDA SAFETY UPDATE

NDA No. 20-819
DRUG: ZEMPLAR INJECTION
(paracalcitol; 19-nor Vitamin D)
INDICATION: Secondary hyperparathyroidism of End Stage Renal Disease
SPONSOR: Abbott Laboratories

SUBJECT: "Recent" Safety Update

The most recent Safety Update to this NDA was submitted in August, 1997. No subsequent update has been filed within the 6 months prior to the final action on this Application.

It is my opinion that no additional safety update data are required since no studies have been ongoing and no additional patients have received the drug since the last update was reviewed.

/S/

Leo Lutwak, M.D., Ph.D.
Medical Officer
April 8, 1998

/S/
4-9-98

CC: NDA Archives
HFD-510/RHedin/GTroendle/LLutwak

APR 7 1998

MEDICAL OFFICER REVIEW OF NDA SAFETY UPDATE

NDA No. 20-819
DRUG:19-nor VITAMIN D_2
Paracalcin Injection
SPONSOR: ABBOTT LABORATORIES
D-389, Bldg. AP30
200 Abbott Park Road
Abbott Park, IL 60064-3537

DATE SUBMITTED: AUG. 1, 1997
DATE RECEIVED CDER: AUG. 4, 1997
DATE RECEIVED, M.O.: AUG. 15, 1997
DATE REVIEWED: APRIL 6, 1998

This submission contains the safety update for the NDA. The studies covered are:
95022: Phase II
95035: Phase III, Multidose
95036: Phase III, Multidose
95037: Phase III, Multidose
95034: Phase III, comparison with intravenous Calcitriol
95028: Phase III, comparison with intravenous Calcitriol
95027: Phase III, comparison with oral Calcitriol
96004: Phase III, open-label
95029: Phase III, open-label

NUMBER OF PATIENTS*

STUDY [N]	DEATHS	OTHER SERIOUS A.E.
95022 [22]	1	6
95035 [31]	2	13
95036 [36]	2	13
95034 [197]	8	87
95037 [16]	2	8
95029 [na]		4
95027 [na]	2	26
95028 [228]	21	156
96004 [na]	8	113
95029 [na]		4

- Number of patients with serious AE, or death. [N] obtained from sources other than this submission. Patients may have head more than one AE.

The causes of death listed and the serious AEs shown are those expected in patients with end-stage renal disease including, cardiac arrest, sepsis, gangrene. Similarly, the serious adverse events were as expected. There were rare cases of hypercalcemia, to be expected with inappropriate dose of vitamin D. Case reports were included only for discontinuations in Study 95034.

No specific action indicated.

/S/

Leo Lutwak, M.D., Ph.D. April 7, 1998
cc: NDA Archives
HFD-510/GTroendle/RHedin/LLutwak

/S/ 4-7-98