CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020819

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology & Biopharmaceutics Review

NDA:	**20-819**	
SUBMISSION DATE:	**January 17, 1997** **April 4, 1997** **October 24, 1997**	MAR 19 1998
BRAND NAME:	**Capthrol™**	
GENERIC NAME:	**Paracalcin Injection** **1, 2 and 5mL ampules**	APPEARS THIS WAY ON ORIGINAL
REVIEWER:	**Carolyn D. Jones, Ph.D.**	
SPONSOR:	**Abbott Laboratories** **Abbott Park, IL**	
Type of Submission:	**Original NDA (NME)**	**Code: 1S**

SYNOPSIS:

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Paracalcin Injection (Capthrol™)19-nor-1 alpha, 25-dihydroxy vitamin D_2 or 19-nor vitamin D_2 analog, is a member of the family of vitamin D compounds, including the naturally-occurring calcitriol. Calcitriol deficiency has been demonstrated in chronic renal failure (CRF) to cause secondary hyperparathyroidism and renal osteodystrophy. Paracalcin Injection is indicated for the prevention and treatment of renal osteodystrophy and secondary hyperparathyroidism encountered with CRF through reduction in parathyroid hormone (PTH) levels by suppression of synthesis and release. The proposed initial dose is _____ administered as a bolus dose no more frequently than every other day (three times each week after each dialysis session). Paracalcin Injection will be packaged in 1, 2 and 5 mL ampules. The dose may be increased by a 0.04 μg/kg/dose at _____ intervals. Serum parathyroid hormone iPTH, calcium (Ca), and Calcium x Phosphorus product should be monitored during titration. The accepted target range for iPTH levels in CRF patients ranges from _____, the non-uremic upper limit of detection. The Ca x P product should not exceed 75.

The sponsor believes that Paracalcin Injection has the advantage over the current therapy in that it can suppress PTH levels with a reduced effect on Calcium (Ca) and Phosphorus (P) metabolism, thereby diminishing the occurrence of hypercalcemia.

The product is only to be given intravenously and the to-be-marketed formulation was used in all

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pharmacokinetic and clinical safety and efficacy studies. Paracalcin pharmacokinetics have been investigated in healthy subjects and in patients with end-stage renal disease (ESRD) requiring hemodialysis (i.e. the target population). Within 2 hours after an intravenous injection, the concentrations decreased rapidly. Thereafter, the drug declined log-linearly with a half-life of about 7 hr in normal subjects and 14 hr in patients with ESRD. No accumulation of paracalcin was observed with multiple dosing (every other day) in patients (up to 0.24 μg/kg) or healthy subjects (up to 0.16 μg/kg).

The linearity of paracalcin could not be determined due to the small number of evaluable subjects/patients in some of the dosage groups that were studied. The effect of gender was studied in patients with no differences observed. Renal function had a substantial effect on paracalcin pharmacokinetics. The AUC was increased _____ patients; clearance was proportionally reduced. When the dose was doubled from _____ 10-fold increase in C_{max} occurred in the patients. The volume of distribution at steady-state (V_{ss}) was 20 L in healthy subjects and 16 L in patients; but the patient values were more variable. The sponsor did not report the occurrence of adverse events for either of the pharmacokinetic studies.

Paracalcin is eliminated primarily by hepatobiliary excretion; 73.7% of the radio-labeled dose was recovered in feces and only 15.8% was found in urine. Several unidentified metabolites were detected in the urine (M-3, M-4 and M-8 account for 51.3% of radioactivity after 48 hours) and feces (M-3, M-4, M-5 and M-7-58.8% fecal radioactivity); unchanged paracalcin was not detected in the urine. The formation pathways, structure and activity of the metabolites are unknown. Plasma protein binding of paracalcin determined in humans *in vitro* was 100% over the concentration range of _____ The mean erythrocyte/plasma ratio was ≤0.04.

RECOMMENDATION:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPEII) has reviewed NDA 20-819 submitted on January 17, 1997. The Human Pharmacokinetics Section is deficient. However, the deficiency will not prevent a decision regarding the approvability of the drug, if the drug is approved based on safety and efficacy _____ Please convey recommendation, comments (p.17) and labeling comments (p.17) to the sponsor as appropriate.

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(Appendices available from DPE-II upon request)

BACKGROUND:

Renal osteodystrophy is an early complication of kidney disease which involves several abnormalities of bone. Elevation of PTH is a major contributor to renal osteodystrophy. The various disorders of bone formation include: fractures and bone deformities, bone cysts, osteopenia, spontaneous tendon rupture, joint pain, myopathy, growth failure in children and metastatic calcification.

Paracalcin Injection (19-nor-1 alpha, 25-dihydroxyvitamin D_2) is a synthetically manufactured analog of calcitriol, the metabolically active form of vitamin D_3. Its empirical formula is given as $C_{27}H_{44}O_3$ which corresponds to a molecular weight of 416.65. The pure drug substance is a white crystalline powder that is insoluble in water.

The drug has not been marketed outside of the United States.

PROTOCOL INDEX

Protocol Number	Title	Page
95018	Pharmacokinetics of 19-nor-1 α, 25-$(OH)_2$-Vitamin D_2 after Single and Multiple Doses in Healthy Volunteers	9
95022	Pharmacokinetics of Paracalcin after Single and Multiple Doses in Patients Requiring Hemodialysis	11
96016	The Metabolism and Excretion of [^{3}H] Abbott 122358 in Healthy Male Volunteers	15
	The *In vitro* Protein Binding of [^{3}H] Abbott 122358 in Mouse, Rat, Dog, Monkey and Human Plasma	15

	In vitro Distribution of [^{3}H] Abbott 122358 Between Erythrocytes and Plasma in Human Blood	**15**
95035	Pharmacokinetics of Paracalcin in Study 95035: Phase III Study: Multidose Evaluation of 19-nor 1α, 25 Dihydroxyvitamin D_2 in End-Stage Renal Disease Patients Undergoing Hemodialysis	**15**
95036	Pharmacokinetics of Paracalcin in Study 95036: Phase III Study: Multidose Evaluation of 19-nor 1α, 25 Dihydroxyvitamin D_2 in End-Stage Renal Disease Patients Undergoing Hemodialysis	**16**
95037	Pharmacokinetics of Paracalcin in Study 95037: Phase III Study: Multidose Evaluation of 19-nor 1α, 25 Dihydroxyvitamin D_2 in End-Stage Renal Disease Patients Undergoing Hemodialysis	**16**

DRUG FORMULATION:

All lots of paracalcin (5 μg/mL) were produced at the Abbott Laboratories facility in Rocky Mount, North Carolina. A single lot of paracalcin (Lot 96-383-DK) was used for all pharmacokinetic/ drug metabolism studies. Paracalcin Injection will be packaged in 1, 2 and 5 mL ampules. The composition of the 5 μg formulation strength is given in Table 1. Table 2 highlights all of the investigational formulations.

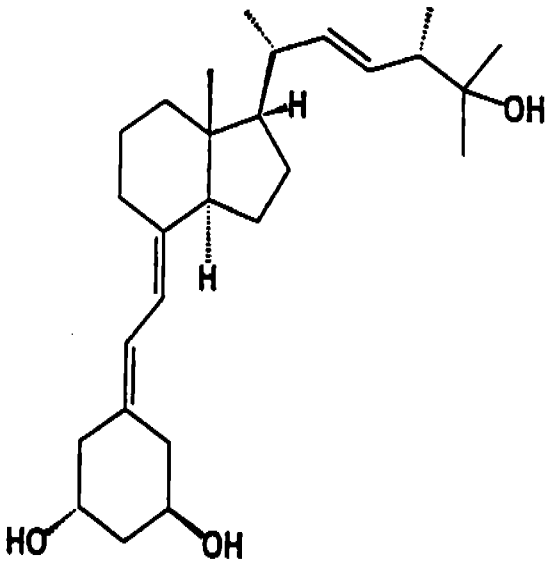

Figure 1: Paracalcin (19-Nor-1α,25-Dihydroxyvitamin D_2)

Table 1 : Theoretical Unit Formulae

Ingredients	Clinical Trial
Paracalcin	
Propylene glycol	
Alcohol	

Paracalcin injection 5 μg/mL is supplied as a single dosage strength in 1, 2 and 5 mL single patient use ampules.

Table 2: Investigational formulations

Study	Dosage (mcg/kg)	Treatment	Lot Number
95003	[redacted]	Paracalcin Injection	96-383-DK
		Placebo*	02-677-DK
95018	[redacted]	Paracalcin Injection	96-383-DK
		Placebo*	02-677-DK
95022	[redacted]	Paracalcin Injection	96-383-DK
		Placebo*	02-677-DK
95028	[redacted]	Paracalcin Injection	15-335-DK and 18-444-DK
		Calcijex®	14-367-DK and 15-147-DK
95029	Investigator Discretion	Paracalcin Injection	15-334-DK
95034	[redacted]	Paracalcin Injection	15-335-DK and 18-444-DK
		Calcijex®	14-367-DK and 15-147-DK

Study	Dosage (mcg/kg)	Treatment	Lot Number
95035		Paracalcin Injection	96-383-DK
		Placebo*	02-677-DK
95036		Paracalcin Injection	96-383-DK
		Placebo*	02-677-DK
95037		Paracalcin Injection	96-383-DK
		Placebo*	02-677-DK
96004	Investigator Discretion	Paracalcin Injection	15-334-DK
96016		Paracalcin Injection	50498-ST-245, specific activity 57.7 Ci/mmol

* Placebo volume equivalent to active drug at respective dose levels.

HUMAN PHARMACOKINETICS AND BIOAVAILABILITY STUDIES

I. Bioavailability/Bioequivalence

This product is only to be given intravenously and the to-be-marketed formulation was studied in both the pharmacokinetic and clinical safety and efficacy studies.

II. Pharmacokinetics

A. Normal Subjects

Study 95018 was conducted to evaluate the safety and PK/PD profiles of paracalcin investigated in 18 normal volunteers (13 males and 5 females) after single and multiple doses of 0.04, 0.08 and 0.16 μg/kg administered in a double-blind, placebo-controlled, randomized, escalating dose fashion. For each group, 4 subjects received drug and 2 received placebo administered IV every other day for a total of 3 doses. Subjects received the drug in an incremental fashion. Incremental increases were a function of total serum Ca level remaining below 11.0 mg/dL and the Ca x P product remaining below 70 as well as the incidence of adverse events. The change in (iPTH) serum parathyroid hormone was measured as a pharmacodynamic parameter. Blood samples for iPTH concentration were collected at screening, prior to the first dose and 48 hr after the last dose. The pharmacokinetics of paracalcin were determined after the first and last dose.

The elimination of the drug was biphasic, and many of the samples (23% at the lowest dose) collected during the terminal phase were below the limit of quantitation. At the 0.16 μg/kg dose, detectable levels were observed up to 24 hours after administration. At the 0.04 μg/kg dose, the last detectable blood level of paracalcin was observed at 8 hours after administration. C_{max} was measured at approximately 8 minutes after administration. As a result of the small sample size, parallel study design, and abundance of samples collected during the terminal phase which were below the limit of detection, the values especially at the 0.04 μg/kg level really represent an approximation of the performace of paracalcin. No determination regarding the linearity of paracalcin could be made. No significant differences in pharmacokinetic parameters nor in accumulation of the drug were observed (Figure 2).

The higher two doses (0.08 and 0.16 μg/kg) did lower serum iPTH concentrations 13% and 35%, respectively (Table 5). A relationship between AUC and % change in serum iPTH concentration was not observed. The results of a covariate analysis (age, race and gender) of the pharmacokinetic parameters showed no correlations with the exception of an increase in normalized AUC with age at the 0.16 μg/kg dose. The sponsor gave no explanation for this observation(Figure 4).

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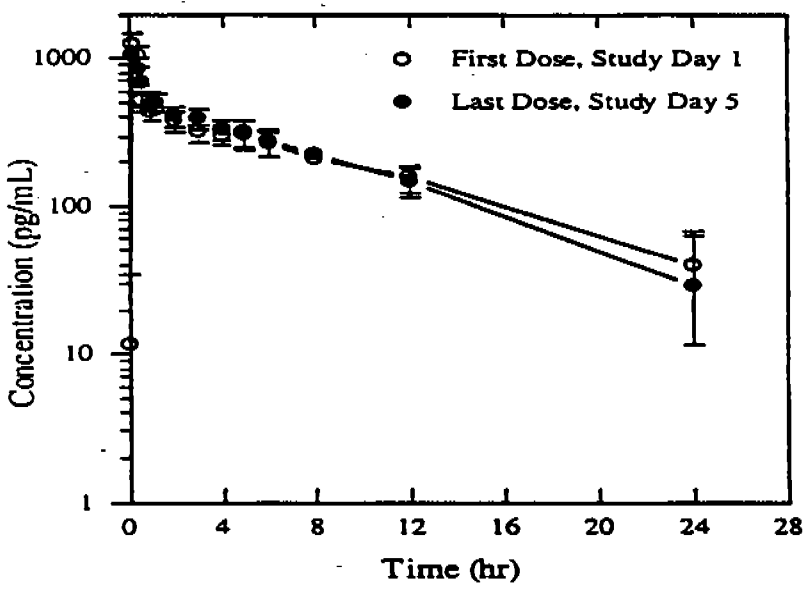

Figure 2: Mean (±SD) Paracalcin Plasma Concentrations after the First and Last Dose of 0.16 μg/kg

Table 4: Paracalcin Pharmacokinetics in Healthy Volunteers taking 0.04, 0.08 and 0.16 μg/kg Doses

Parameter	Dose (μg/kg) 0.04	0.08	0.16
First Dose (Study Day 1)			
C_{max} (pg/mL)	256 ± 44	664 ± 146	1242 ± 226
$AUC_{0-\infty}$ (pg·hr/mL)	683 ±165	2221 ± 401	5247 ± 893
CL (L/hr)	4.2 ± 2.1	2.7 ± 0.6	2.4 ± 0.4
$t_{1/2}$ (hr)[H*]	2.7 ± 0.4	5.3 ± 1.3	7.3 ± 1.0
V_{ss} (L)	17 ± 10	20 ± 6	23 ± 2
Third Dose (Study Day 5)			
C_{max} (pg/mL)	232 ± 51	553 ± 137	1061 ± 117
$AUC_{0-\infty}$ (pg·hr/mL)	1077 ± 343	2104 ± 726	5331 ± 939
CL (L/hr)	2.5 ± 0.1	3.0 ± 1.2	2.4 ± 0.3
$t_{1/2}$ (hr)[H]	5.6 ± 4.9	4.8 ± 1.7	6.8 ± 1.2
V_{ss} (L)	25 ± 17	20 ± 2	22 ± 3

[H] Harmonic means and pseudo standard deviations; the arithmetic means ± SD after doses of 0.04, 0.08, and 0.16 μg/kg were 2.7 ± 0.4, 5.7 ± 1.9, and 7.4 ± 0.9 hr after the first dose and 7.1 ± 4.5, 5.4 ± 2.3, and 7.0 ± 1.0 hr after the last dose, respectively.

* Statistically significant difference between dose groups (based on statistical analysis of β, p = 0.0007).

Note: For the 0.04 μg/kg dose group, n = 2 for all parameters except for C_{max}, where n = 4.

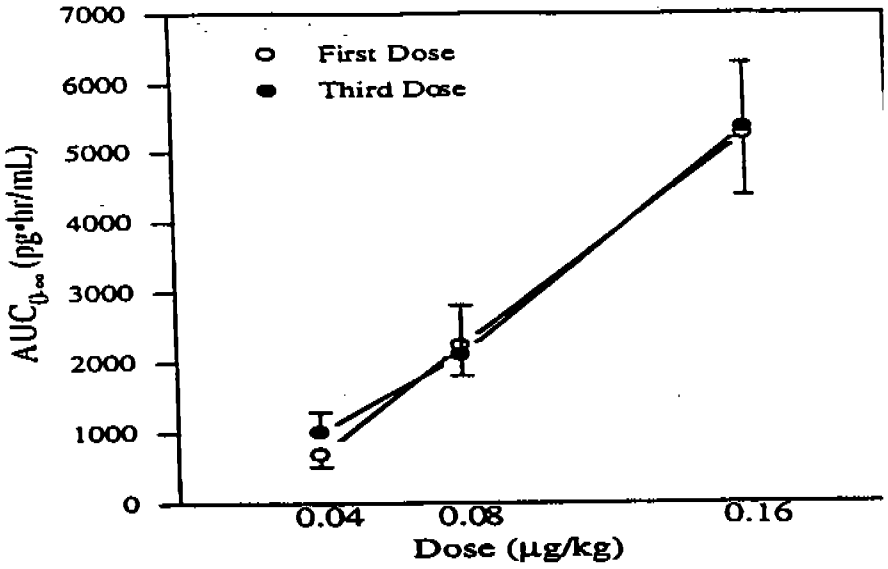

Figure 3: Mean (SD) AUC of Paracalcin after 0.04, 0.08 and 0.16 µg/kg Single and Multiple Intravenous Dosing in Healthy Volunteers

Table 5: Mean ±SD Serum iPTH Concentrations (pg/ml) of Paracalcin at 0.04, 0.08, and 0.16 µg/kg Doses

Mean ± SD Serum iPTH Concentrations (pg/mL)		
Screening	Prior to First Dose	48 hr After Last Dose
Group 1 (0.04 µg/kg paracalcin)		
19.8 ± 13.1	34.3 ± 14.2	18.5 ± 11.8
Group 2 (0.08 µg/kg paracalcin)		
17.3 ± 7.1	17.5 ± 5.2	15.3 ± 7.9
Group 3 (0.16 µg/kg paracalcin)		
21.0 ± 8.6	17.5 ± 6.0	12.3 ± 6.0
Subjects Receiving Placebo		
25.2 ± 4.7	25.0 ± 8.9	24.2 ± 4.5

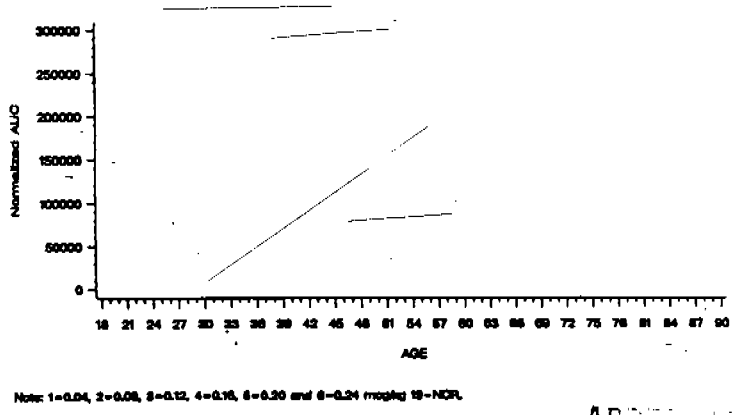

Figure 4: Plot of Dose Normalized AUC vs. Age by Dose Following First Dose of 19-NOR Study 95022

B. Patients

Of the 22 ESRD patients recruited to participate in the single and multiple dose double-blind, placebo-controlled, escalating dose study, the pharmacokinetics of paracalcin were evaluated in 16 patients (8 males and 8 females). Patients received three times a week for four weeks an intravenous bolus dose after each hemodialysis session. Patients received in a randomized and incremental fashion paracalcin doses of 0.04, 0.08, 0.16 and 0.24 μg/kg for groups 1-4 respectively.

As in normal subjects, elimination was biphasic with the distribution phase essentially complete 2 hours after the dose. After the first dose administration, only one patient was evaluable at the 0.08μg/kg dose and no patients were evaluable at 0.16μg/kg dose. As a result it was difficult to evaluate the linearity of the drug. The AUC and C_{max} values suggested the possibility of linear kinetics, but this was not apparent in lower dosages (Table 6). No statistically significant differences in gender were observed ($p>0.47$) (Figure 6). There was no evidence of paracalcin accumulation after each dialysis session. The dialyzability of paracalcin was not demonstrated in this study.

In eight of the twelve concentration vs. time profiles, the half-life could not be accurately estimated because many of the data points fell below the lower limit of quantitation. On the otherhand, the highest dose achieved measurable concentrations up to 44 hours. In healthy volunteers, half-life approximated 7 hours and end-stage renal disease patients had a half-life of 14 hours.

The pharmacokinetic parameters were significantly altered in patients compared to healthy volunteers. AUC was increased _____ patients. Clearance was proportionally reduced. When the dose was doubled from_____ a 10 -fold increase in C_{max} occurred (Table 6).

The comments that no accumulation occurred were based on the data for the lowest and highest doses (0.04 and 0.24 μg/kg), and the fact that the concentrations that were measured immediately prior to the last dose were below the limit of quantitation.

Several design considerations were taken into consideration upon review and evaluation of these two studies. First of all, the studies were parallel in design, the sample sizes for the dose groupings in the studies were very small and ranged from a maximum of 6 to a minimum of 1 patient. Secondly, the majority of the samples were collected during the distribution phase during a very narrow time frame.

The integrity of the study is also in question because discrepancies were identified regarding the collection times of the pharmacokinetic samples. Approximately 25% of the sample times were not obtained within 10% of the designated times after the dose. Two patients had samples taken either 44 hours after the designated time and one patient had an extremely high pre-dose sample which indicated the sample was actually taken after administration of the dose. Although the protocol specified a 6 hr sample collection, none of the patients had a sample collected.

Table 6: Paracalcin Pharmacokinetics in Patients taking 0.04, 0.08, 0.16 and 0.24 µg/kg Doses

Parameter	Dose (µg/kg) 0.04	0.08	0.16	0.24
	After the First Dose Administration			
N*	6: 2	1: 0	0: 0	6: 4
C_{max} (pg/mL)	264 ± 101	716	-	1951 ± 831
$AUC_{0-\infty}$ (pg*hr/mL)	7391 ± 3168	NE	-	28671 ± 11091
CL (L/hr)	0.60 ± 0.41	NE	-	0.60 ± 0.19
$t_{1/2}$ (hr)^H	45.3 ± 33.9	NE	-	14.2 ± 2.7
V_{ss} (L)	38 ± 6	NE	-	5 ± 2
	After the Last Dose Administration			
N*	6: 2	2: 2	1: 1	5: 3
C_{max} (pg/mL)	242 ± 91	2127 ± 1972	4566	1728 ± 455
$AUC_{0-\infty}$ (pg*hr/mL)	4798 ± 2382	14399 ± 11340	18232	25662 ± 3301
CL (L/hr)	0.78 ± 0.10	0.58 ± 0.29	0.91	0.87 ± 0.25
$t_{1/2}$ (hr)^H	24.7 ± 11.4	11.3 ± 16.2	25.0	13.0 ± 1.0
V_{ss} (L)	29 ± 10	9 ± 5	31	7 ± 2

* Total number of patients (used in the calculation of mean C_{max}); number of patients for whom β could be estimated (used in the calculation of all other parameters).
NE: Not evaluable.
H Harmonic means and pseudo standard deviations.

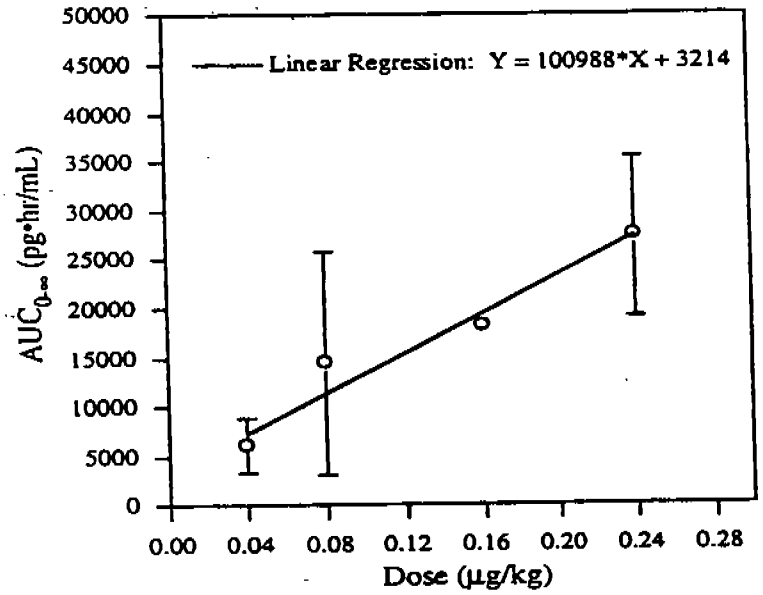

Figure 5: Paracalcin Mean (±SD) $AUC_{0-\infty}$ Values vs. Dose

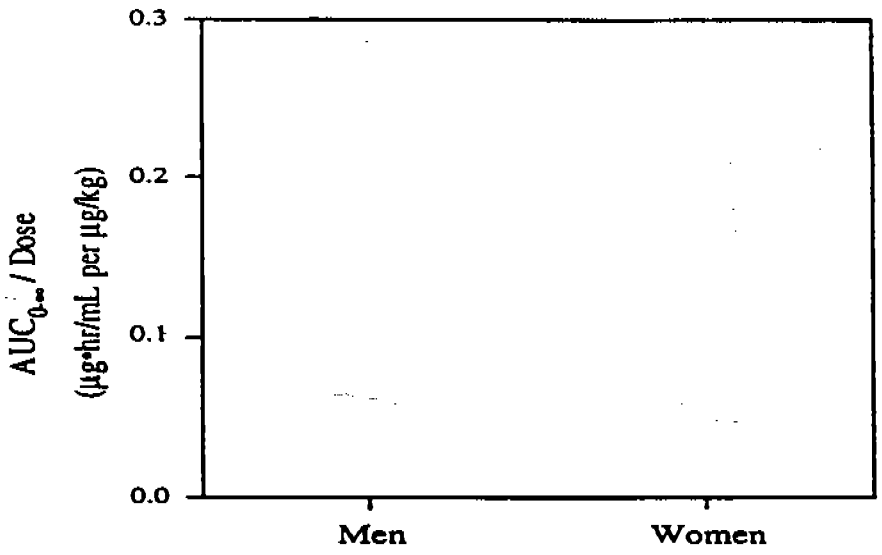

Figure 6: Effect of Gender in Paracalcin Pharmacokinetics in Patients

III. Metabolism

In the mass balance study in which paracalcin was administered intravenously, only 89.5% of the total dose radioactivity was recovered in excreta 7 to 10 days post-dose. Of that, 73.7% was found in the feces between 48 and 120 hr after administration and 15.8% was recovered in the urine over 7-10 days. Based on this information, the drug probably undergoes biliary excretion. Similarity existed between humans and dogs, but not rats.

Parent drug was the only significant radioactive component detected in the plasma in humans, rats and dogs. After administration of an intravenous bolus _____ the terminal elimination half-life was 21.0 hours and $AUC_{0\text{-}24}$ was 7.2 ng•h/mL. Biotransformation of paracalcin was extensive with parent drug accounting for 8% of the fecal radioactivity and 5.7% of the total dose radioactivity. Unknown metabolites found in human feces were M3, M4, M5 and M7 with the corresponding contribution to fecal radioactivity of 10.4%, 11.4%, 23.0% and 6.0%. Also in humans were several other unknown _____; that had retention times similar to fecal metabolites observed in dogs. The sponsor suggested that these unknown peaks represent by-products of microbial degradation of certain biliary metabolites in the gastrointestinal tract.

The parent compound was not found in any of the _____ urine samples, however three metabolites M3, M4 and M8 contributed means of 27.5%, 7.6% and 16.2% of the urinary radioactivity (total 51.3%). There was some interspecies differences regarding formation of urinary metabolites. M-3 was the major urinary and fecal metabolite in rats. However, human and dog metabolites formed were similar. Unknown peaks in urine were treated with β-glucuronidase and the peaks disappeared suggesting they were glucuronide conjugates. However, the major metabolite M-3, was not affected by the hydrolyzing enzymes. The sponsor has not identified the structure, activity or formation pathways for the various metabolites.

In vitro binding results were the same in humans as in animals (>99.9%) over the drug concentration range _____ No gender differences in binding were observed. The extraction of paracalcin by hemodialysis is unlikely because of this high protein binding.

The distribution of paracalcin into the erythrocyte and plasma was determined over the concentration range _____ The ratio of whole blood to plasma was 0.54, indicating the drug resides in plasma. The red blood cells to plasma ratio was ≤0.04. The fraction in whole blood bound to red blood cells was ≤0.02. The human data was comparable to animal data.

IV. Pharmacodynamic Studies

The pharmacodynamic measurement for this drug was serum iPTH as the primary efficacy variable. A 30% decrease from baseline was a demonstration of efficacy. The secondary efficacy parameter was serum alkaline phosphatase.

Three Phase III studies were conducted in which up to 4 blood samples were collected. The first was a multidose evaluation of 19-nor-1 alpha, 25-Dihydroxyvitamin D2 in end stage renal disease patients undergoing hemodialysis. Of the patients enrolled in the study, 23 (12 men and 11 women) had blood samples drawn for pharmacokinetic analysis. The study was double-blind and placebo-controlled. For 12 weeks, patients received a dose three times each week after hemodialysis. Blood samples were collected 2, 24 and 44 hr after the last dose (Week 12).

The mean paracalcin concentrations were somewhat higher in this study after the 0.04μg/kg dose compared to values obtained in the Phase II patient study. This difference could be attributed to the variability of the clinical trial data. At higher doses, however, the values were similar.

In the second study, patients were given an incremental dose increase every two weeks to a maximum of 5 increases if necessary to lower serum iPTH levels. The study was conducted at three different study sites. Thirty patients were enrolled and 22 patients (12 males and 10 females) had blood samples drawn for PK analysis. As seen in other studies, distribution occurred at approximately 2 hours. The concentrations were similar in this study compared to data obtained in phase II studies.

No relationship between the dose of a patient required to cause a 30% decrease in iPTH could be predicted on baseline iPTH values. Of twenty-seven paracalcin-treated patients who had at least a 30% decrease in iPTH for at least four blood draws, one patient achieved a 30% decrease on 0.04 µg/kg paracalcin, nine on 0.08 µg/kg, eight on 0.12 µg/kg, six on 0.16 µg/kg and three on 0.20 µg/kg of paracalcin. The optimum dose is probably around _____ of paracalcin.

In the third study, approximately 30 subjects were to be enrolled. Of these 12 (5 males and 7 females) had blood samples drawn for PK analysis. A sample mix-up occurred at one of the sites and 4 subjects who were supposed to receive placebo actually received paracalcin and vice versa for a total of 8 subjects involved in the mishap. An additional sample was to be collected post-dialysis and prior to the dose. Three subjects had recorded times of sample collection five minutes prior to the scheduled dose. However, when the samples were analyzed, it was apparent that the samples were collected after administration of the dose because of the high levels of paracalcin present. Another subject had an extremely high 24 hr reading that was more reflective of a sample collected immediately after administration of the dose. Because of the difficulties associated with the conduct of this study, the results of this third study will not be used in the overall review of this drug.

The sponsor stated that an audit of all the studies (95035, 95036 and 95037) was conducted. Clinical supplies for the first two studies were assembled at the same time. Study 95037 was assembled at a later date. Therefore, this latter study was the only one impacted by the various miscues.

COMMENTS FROM THE MEDICAL OFFICER REGARDING THIS SUBMISSION:

Paracalcin shows efficacy in the suppression of iPTH levels. The indication for prevention and treatment of renal osteodystrophy is not supported by the data submitted. The assumption that prevention of elevation of iPTH levels will lead to prevention of bone diseases must be supported by data such as: bone biopsy, skeletal x-rays, measurements of bone mineral density and biochemical indices of bone turnover. Therefore, the Agency is recommending approval only for the secondary hyperparathyroidism indication. Only marginal differences exist between paracalcin and calcitriol. Therefore, the claims of superiority cannot be made. Although not statistically significant, paracalcin may carry lower risks of hypercalcemia.

COMMENTS TO THE MEDICAL OFFICER:

1. In the **DOSAGE AND ADMINISTRATION section** of the label, the second sentence should be changed.

"The recommended initial dose or Trade Name depending on the severity of the secondary hyperparathyroidism, is 0.04 mcg/kg to 0.24 mcg/kg administered as a bolus dose no more frequently than every other day."

The sponsor has not submitted any data that indicates a relationship between dose and baseline iPTH levels. The reviewing medical officer should provide revised language in this regard.

2. As part of the pharmacokinetic study report, it is customary to include a report of adverse events which was not included in the two pharmacokinetic studies submitted as part of this NDA.

LABELING COMMENTS:

1. Many of the comments below are formatting comments consistent with current suggestions for the presentation of labeling information.

CLINICAL PHARMACOLOGY

Mechanism of Action

Paracalcin is a vitamin D...

Pharmacokinetics:

Distribution

The pharmacokinetics of paracalcin...

Elimination

In healthy subjects, plasma radioactivity....

Metabolism

Several metabolites were detected ...

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

Parameter	n	Values (Mean ±SD)
C_{max} (8 min after bolus)	6	1850 ± 664 (pg/mL)
$AUC_{0-\infty}$	5	27382 ± 8230 (pg•hr/mL)
CL	5	0.72 ± 0.24 (L/hr)
V_{ss}	5	6 ± 2 (L)
$t_{½}$ †	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. The pharmacokinetics were not race or gender-dependent.

Drug Interaction: Specific interaction studies were not performed;

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DRAFT LABELING

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3/3/98
Carolyn D. Jones, Ph.D.
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

RD initialed by Hae-Young Ahn, Ph.D., Team Leader 3/11/98
OCPB Briefing: March 19, 1998 Attendees: Jones, Ahn, M. Chen, Ajayi and Lutwak

FT initialed by Hae-Young Ahn, Ph.D., Team Leader /S/ 3/19/98

cc: NDA 20-819 (1 copy) HFD-510 (Lutwak, Hedin), HFD-340 (Vishwananthan), HFD-870 (Ahn, Jones, M. Chen), CDR (Murphy).

CODE: **AE**