CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-606

PHARMACOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	**21-606**
SERIAL NUMBER:	**000**
DATE RECEIVED BY CENTER:	**7/28/04**
PRODUCT:	**Zemplar (paricalcitol) capsule**
INTENDED CLINICAL POPULATION:	**Secondary hyperparathyroidism associated with chronic kidney disease (stage 3, 4)**
SPONSOR:	**Abbott**
DOCUMENTS REVIEWED:	**EDR**
REVIEW DIVISION: **(HFD-510)**	**Division of Metabolic & Endocrine Drug Products**
PHARM/TOX SUPERVISOR:	**Karen Davis-Bruno**
DIVISION DIRECTOR:	**David Orloff**
PROJECT MANAGER:	**Randy Hedin**

Date of review submission to Division File System (DFS): 2/4/05

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EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability: Approval (AP) pending labeling changes

B. Recommendation for nonclinical studies: none

C. Recommendations on labeling

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 104-week carcinogenicity study in CD-1 mice, an increased incidence of uterine leiomyoma and leiomyosarcoma was observed at subcutaneous doses of 1, 3,10 mcg/kg given three times weekly — times the exposure following a human dose of 14 mcg, equivalent to 0.24 mcg/kg based on AUC). The incidence rate of uterine leiomyoma was significantly different than the control group at the highest dose of 10 mcg/kg. In a 104-week carcinogenicity study in rats, there was an increased incidence of benign adrenal pheochromocytoma at subcutaneous doses of
0.15, 0.5, 1.5 mcg/kg (< 1 to 7 times the exposure following a human dose of 14 mcg, equivalent to 0.24 mcg/kg based on AUC). The increased incidence of pheochromocytomas in rats may be related to the alteration of calcium homeostasis by paricalcitol. Paricalcitol did not exhibit genetic toxicity *in vitro* with or without metabolic activation in the microbial mutagenesis assay (Ames Assay), mouse lymphoma mutagenesis assay (L5178Y), or a human lymphocyte cell chromosomal aberration assay. There was also no evidence of genetic toxicity in an *in vivo* mouse micronucleus assay. Paricalcitol had no effect on fertility (male or female) in rats at intravenous doses up to 20 mcg/kg/dose (equivalent to 13 times a human dose of 14 mcg based on surface area, mcg/m2).

Pregnancy

— *Pregnancy category C*

Paricalcitol has been shown to cause minimal decreases in fetal viability (5%) when administered daily to rabbits at a dose 0.5 times a human dose of 14 mcg or 0.24 mcg/kg (based on body surface area, mcg/m2), and when administered to rats at a dose two times the 0.24 mcg/kg human dose (based on body surface area, mcg/m2). At the highest dose tested, 20 mcg/kg administered three times per week in rats (13 times the 14 mcg human dose based on surface area, mcg/m2), there was a significant increase in the mortality of newborn rats at doses that were maternally toxic and are known to produce hypercalcemia in rats. No other effects on offspring development were observed. Paricalcitol was not teratogenic at the doses tested.
Paricalcitol (20 mcg/kg) has been shown to cross the placental barrier in rats.
There are no adequate and well-controlled clinical studies in pregnant women. Zemplar® Capsules should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

Studies in rats have shown that paricalcitol is present in the milk. It is not known whether paricalcitol is excreted in human milk —

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings: Effects related to paricalcitol's calcemic activity include extraskeletal calcification, renal pathology, increases in serum BUN and creatinine, anorexia with decreased body weight gain, increased adrenal weight, alkalosis and hyperostosis. These effects are consistent with prolonged elevations in serum calcium (and possibly phosphorus) and would not be expected in the clinic since serum calcium and phosporus are monitored routinely during vitamin D therapy and treatment can be modified as necessary.
Additional effects unrelated to hypercalcemia include decreased WBCs, thymic atrophy and increased PTT in dogs (PTCC is decreased in rats). These effects have not been seen in humans.

B. Pharmacologic activity: Paricalcitol is a synthetic biologically active vitamin D analogue of calcitriol that selectively upregulates the vitamin D receptor in the parathyroid gland without causing receptor upregulation in the intestine. It is less active on bone resorption than calcitriol.

C. Nonclinical safety issues relevant to clinical use: none

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

Zemplar (paracalcitol) was approved in 1998 under NDA 21-819 as an intravenous 0.04-0.1 μg/kg (2.8-7 μg) every other day for the prevention and treatment of secondary hyperparathyroidism associated with chronic renal failure. A complete nonclinical development program was performed under NDA 20-819. Most studies utilized IV or SC dosing. The current NDA 21-606 cross references the original NDA 20-819 in addition to providing additional drug metabolism reports and a one month rat and dog oral toxicity study reviewed under IND 60, 672 in order to bridge to the nonclinical studies in approved NDA 20-819.

NDA number: 21-606
Review number: 1
Sequence number/date/type of submission: 000
Information to sponsor: Yes (X) No ( ) labeling
Sponsor and/or agent: Abbott
Manufacturer for drug substance: Abbott

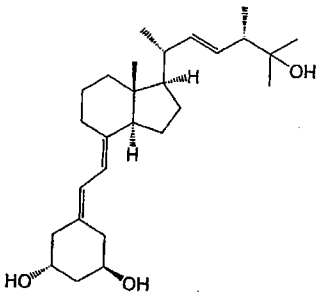
Reviewer name: Davis-Bruno
Division name: DMEDP
HFD #: 510
Review completion date: 2/4/05

Drug:

Trade name: Zemplar capsules
Generic name: paracalcitol
Code name: A-122358; ABT-358
Chemical name: 19-nor-1α,25 dihydroxy-vitamin D2

Molecular formula/molecular weight: 416.64 g/mole
Structure:

Figure 1. **Structural Formula of Paricalcitol (alternatively 19-nor-1 alpha, 3 beta, 25-trihydroxy-9,10-secoergosta-5(Z),7(E),22(E)-triene)**



Relevant INDs/NDAs/DMFs: NDA 20-819 (intravenous) AP; IND 60,672 oral, IND 47,713 injectable

Drug class: synthetic calcitriol (vitamin D) analogue

Intended clinical population: secondary hyperparathyroidism associated with chronic kidney disease (stage 3, 4)

Clinical formulation: capsules 1, 2, 4 µg every other day. The capsule fill solution is paricalcitol — with — alcohol and is essentially the same as that used in nonclinical oral studies.

Route of administration: oral

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Data reliance : Except as specifically identified below, all data and information discussed below and necessary for approval of NDA 21-606 are owned by Abbott or are data for which Abbott has obtained a written right of reference. Any information or data necessary for approval of 21-606 that Abbott does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that Abbott does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of NDA 21-606.

Studies reviewed within this submission: one month oral rat, dog toxicology studies originally reviewed under IND 60,672 and new drug metabolism studies pertaining to the oral formulation an overview of the PK data is below.

APPEARS THIS WAY
ON ORIGINAL

1.0 Pharmacokinetics Tabulated Summary

1.1 Pharmacokinetics Overview

Test Article: Paricalcitol (A-122358.0)

Type of Study	Test System	Method of Administration	Testing Facility	Study Number
Absorption†	SD Rat	p.o. & i.v.	Abbott Labs, Abbott Park, IL	R&D/03/047
	Beagle Dog	p.o. & i.v.	Abbott Labs, Abbott Park, IL	R&D/03/047
	Human Caco-2	*In vitro*	Abbott Labs, Abbott Park, IL	R&D/02/710
Distribution	SD & LH Rat	i.v.	/	R&D/96/423
	SD & LH Rat	p.o.		R&D/02/188
	Mouse, Rat, Dog, Monkey, Human Plasma	*In vitro*	Abbott Labs, Abbott Park, IL	R&D/95/952
	Human blood	*In vitro*	Abbott Labs, Abbott Park, IL	R&D/95/989
	Human plasma	*In vitro*	Abbott Labs, Abbott Park, IL	R&D/99/529
	Human plasma	*In vitro*	Abbott Labs, Abbott Park, IL	R&D/02/775
	Human plasma	*In vitro*	Abbott Labs, Abbott Park, IL	R&D/04/201
	Pregnant Rat	p.o.		R&D/04/187
	Lactating Rat and Pups	p.o.	/	R&D/04/188

Type of Study	Test System	Method of Administration	Testing Facility	Study Number
Metabolism & Excretion	SD Rat	i.v.	Abbott Labs, Abbott Park, IL	R&D/95/937
	Beagle Dog	*i.v.*	Abbott Labs, Abbott Park, IL	R&D/96/572
	Human	i.v.	[redacted]	R&D/96/677
	SD Rat	i.v. & p.o.	Abbott Labs, Abbott Park, IL	R&D/00/367
	Human	i.v. & p.o.	[redacted]	R&D/02/890
	Beagle Dog	p.o. & i.v.	Abbott Labs, Abbott Park, IL	R&D/03/044
	SD Rat	i.v. & p.o.	[redacted]	R&D/04/277
Metabolism	Liver/Kidney Slice, Microsomes, S-9, Carcinoma Cell Lines, Expressed Rat CYP24	*In vitro*	Abbott Labs, Abbott Park, IL	R&D/03/043
	Human Liver Microsomes	*In vitro*	Abbott Labs, Abbott Park, IL	R&D/04/276

SD – Sprague-Dawley derived rat; LH – Lister Hooded derived rat.
† most dose pharmacokinetic studies may be found in R&D/03/075

Studies not reviewed within this submission: N/A
Note: For NDA reviews, all section headings should be included.

2.6.2 PHARMACOLOGY

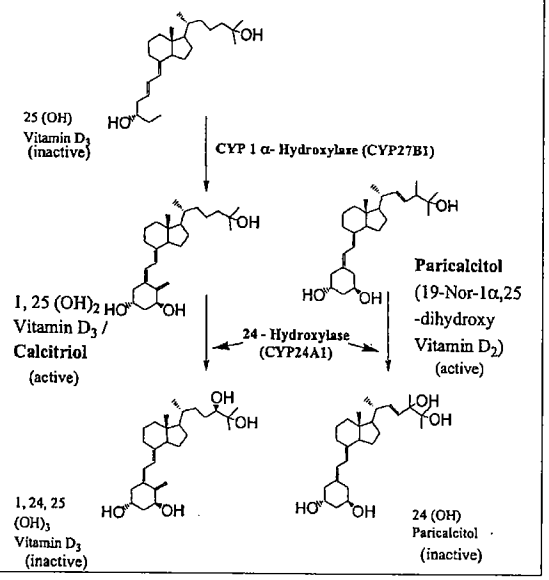
2.6.2.1 Brief summary see NDA 20-819

2.6.2.2 Primary pharmacodynamics

Mechanism of action: Paricalcitol is a synthetic biologically active vitamin D analogue of calcitriol that selectively upregulates the vitamin D receptor in the parathyroid gland without causing receptor upregulation in the intestine. It is less active on bone resorption than calcitriol. Paricalcitol has less bone resorbing activity than calcitriol in stimulated mouse marrow osteoclasts and is 7-10-fold less effective than calcitriol in mobilizing calcium and phosphorus from bone. Data in mouse calivariae indicate that while both

drugs have similar effects on calcium efflux from bone, paricalcitol does not appear to inhibit osteoblast activity at therapeutic concentrations.
Paricalcitol upregulates the calcium sensing receptor in the parathyroid gland inhibiting parathyroid proliferation, decreasing PTH synthesis and secretion with minimal impact on calcium and phosphorus (5-fold less effective than calcitriol). Any reduction in the expression of 24-hydroxylase is expected to reduce the clearance of paricalcitol.

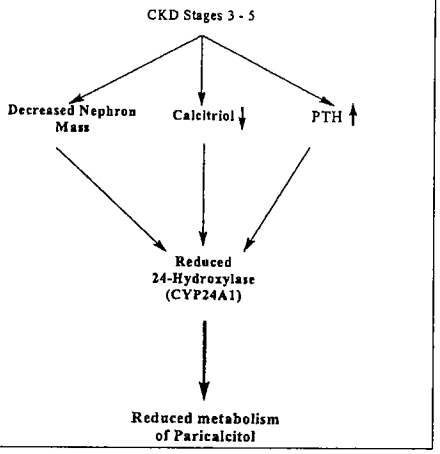
Figure 22. **Metabolic Pathway of 25 (OH)Vitamin D_3 and Paricalcitol**



Drug activity related to proposed indication: Secondary hyperparathyroidism is associated with inadequate active vitamin D. In diseased kidneys the activation of vitamin D is diminished resulting in increased PTH and subsequent abnormalities in serum calcium and phosphorus, adversely affecting bone turnover and may result in renal osteodystrophy. In chronic kidney disease reductions in PTH result in favorable bone physiology.

A study in nephrectomized rats showed that the 24-hydroxylase levels are decreased by 4-fold in 4 weeks and 8-fold in 8 weeks. There was a reciprocal increased in 1α-hydroxylase which might serve to maintain the circulating calcitriol. In CKD a progressive loss of nephron mass occurs which contributes to the decrease in renal 24-hydroxylase which plays a key homeostatic role in calcitriol and paricalcitol metabolism.

Explanation of Reduced Paricalcitol CL in CKD Stage 3–5 Subjects



2.6.2.3 Secondary pharmacodynamics see NDA 20-819

2.6.2.4 Safety pharmacology see NDA 20-819

2.6.2.5 Pharmacodynamic drug interactions only human in vitro data provided see Biopharm review of NDA 21-606

2.6.3 PHARMACOLOGY TABULATED SUMMARY SEE NDA 20-819

2.6.4 PHARMACOKINETICS/TOXICOKINETICS
see NDA 20-819

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2.6.4.1 Brief summary: Sprague-Dawley rats were given 3 μg/kg (1.5 ml/kg) bolus IV paricalcitol via juglar vein, or 3 μg/kg or 20 μg/kg oral by gavage. Beagle dogs received 0.3 μg/kg bolus IV via cephalic vein or another group given the same dose but in a solution of —— (clinical formulation) by capsules, a third group received 1 μg/kg oral capsules. A low volume of distribution (0.17-0.19 L/kg) and plasma clearance (0.04 male rat, dog to 0.1 L/h kg female rat) was determined for both rat and dog. Terminal elimination half-life ranged from 1.2 h following a 3 μg/kg IV dose in female rats to 3.5 h following 0.3 μg/kg in dog. Differences in gender PK profile were observed in rats following IV dosing. Male rats provided a longer terminal elimination half-life (2.3 vs. 1.2 h), lower plasma clearance (0.04 vs. 0.1 L/h kg) and 2-fold higher AUC (73.76 vs. 34.44 ng h/ml) after a 3 μg/kg IV dose compared to females. The volume of distribution was similar. There were no significant gender differences in exposure after single oral dosing in rat. However since AUC in male rats after IV dosing was higher than females at an equivalent dose the apparent oral bioavailability in males was lower (17.5% vs. 32.4% at 3 μg/kg and 8.8% vs. 19.1% at 20 μg/kg) than female rats. There were no gender differences following IV dosing in dogs. The PK profile in dog is similar to male rats.

2.6.4.2 Methods of Analysis

See NDA 20-819 review

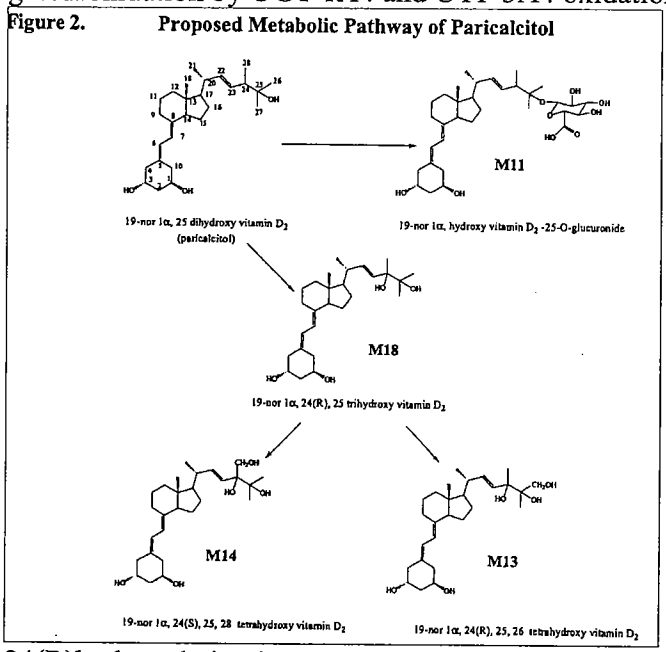
2.6.4.3 Absorption : In vitro protein binding (1-100 ng/ml) was 99.9-100% in rat, mouse, dog, monkey and >99.8% in healthy humans. Distribution into erythrocytes (0.01-10 ng/ml) relative to plasma was 0-0.04 suggesting that distribution into cellular blood fractions was minimal.

Absorption studies with human Caco-2 cells suggest that paricalcitol is primarily abosprbed by passive diffusion through the GI tract and is not a high affinity substrate for active transporters; P-glycoprotein.

2.6.4.4 Distribution : Radioactivity in rats reached a maximum at 1 h post-dose where pituitary, thyroid, whole blood, heart, pancreas, salivary gland, bone marrow, subcutaneous rat and bladder had the highest levels. At 4 hr. post dose the Harderian gland, kidneys, and testes had the highest level and by 8h the liver. Radioactivity in plasma and tissues declined by 96 h post-dose when only the concentrations in liver and kidneys exceeded the plasma.

2.6.4.5 Metabolism: Circulating metabolites include M18 (24(R) hydroxy metabolite) and M24 a less polar metabolite. M18 is less potent than parent in rats. M18 and M24 are circulating human metabolites that are present in rat and dog plasma after oral dosing. Eleven metabolites (>2% biliary radioactivity) were measurable in dog bile. These metabolites were similar to those detected in human urine and feces although the identity of the majority has not been established. M11 is the parent glucuronide, other characterized metabolites include M13, M14 and M18 is from in vitro studies which indicate that the dog and rat are qualitative representatives of human metabolism based on microsome, hepatocytes and liver and kidney slice studies. Hydroxylation by renal CYP24A1 hydroxylase and non-renal CYP 24A1 hydroxylase (skin, bone, GI), direct glucuronidation by UGT 1A4 and CYP 3A4 oxidation have been identified.

Figure 2. Proposed Metabolic Pathway of Paricalcitol



24(R)hydroxylation is suspected to occur by CYP2A and a hepatic microsomal pathway. In dog kidney further oxidation of this metabolite (M18) by additional oxidations at either carbon 26 or 28 can form primary alcohols which can undergo glucuronide and/or sulfoconjugation in the liver. Selective CYP3A inhibitors can block human microsomal formation of M18. Further studies are ongoing to understand the relative importance of this pathway compared to CYP2A (renal, non-renal) and glucuronidation in metabolism of paricalcitol in stage 5 CKD patients. The ability of paricalcitol (5-50 nM; 2-21 ng/ml) to inhibit CYP 3A4, 1A2, 2A6, 2B6, 2C8, 2C19, 2D6 and 2E1 revealed no inhibition at the concentrations tested. P450 induction at up to 50 nM was <2-fold. Based on low circulating plasma concentrations (0.3 ng/ml; <1 nM) and high protein binding paricalcitol is unlikely to produce significant drug metabolic interactions.

Two excretory metabolites M7 (fecal only) and M8 (renal, hepatobiliary) have been indentified in vitro but low pharmacological dose of the drug has prevented full characterization in humans (in vivo).

2.6.4.6 Excretion : is primarily biliary/fecal as confirmed by bile duct cannulated rats and dogs. CYP24A1 and CYP3A4 are presumed to account for the majority of human clearance with 2% of the parent dose eliminated as M11, aglycone, glucuronidation (<5%).

2.6.4.7 Pharmacokinetic drug interactions N/A

2.6.4.8 Other Pharmacokinetic Studies

1.7 Pharmacokinetics: Study In Pregnant or Nursing Animals

Test Article: Paricalcitol

Study No. R&D/04/187

Species: Sprague Dawley Rat
Gender (M/F)/Number of Animals: Pregnant female time mated (Day 17 of gestation)/18 (3 per time point)
Feeding Condition: Fasted
Vehicle/Formulation: [redacted]
Method of Administration: Oral
Dose (µg/kg): 20
Radionuclide: ^{3}H
Specific Activity: 5.171 µCi/µg
Sampling Time: 1, 4, 8, 12, 24 and 48 hours post dose

Tissues/Organs	Concentration (ng equivalents/g)					
	1 hr	4 hr	8 hr	12 hr	24 hr	48 hr
Amniotic Fluid (mL)	0.51	0.59	0.75	0.78	0.64	0.37
Total Fetus	0.41	0.49	0.51	0.57	0.34	0.28
Kidneys	4.59	3.68	2.16	1.65	0.88	0.49
Liver	9.57	24.44	28.93	20.41	7.46	1.29
Lungs	5.00	9.04	1.13	0.99	0.46	0.22
Mammary Gland	2.97	2.83	2.56	1.72	0.99	0.47
Ovaries	3.15	1.73	0.97	0.77	0.33	0.17
Placenta	2.43	1.88	1.26	1.53	1.23	0.84
Skin	1.13	1.04	0.75	0.76	0.29	0.12
Uterus	3.02	2.35	1.73	1.71	1.02	0.46
Whole Blood	2.69	3.01	1.63	1.42	0.56	0.20
Plasma (mL)	12.47	5.30	2.54	2.21	0.89	0.31

1.7 Pharmacokinetics: Study in Pregnant or Nursing Animals (cont'd)

Test Article: Paricalcitol

Study No. R&D/04/188

Species: Sprague Dawley Rat
Gender (M/F)/Number of Animals: Pregnant female time mated/12 (3 per time point)
Feeding Condition: Fasted
Vehicle/Formulation: —
Method of Administration: Oral
Dose (µg/kg): 20
Radionuclide: ^{3}H
Specific Activity: 5.426 µCi/µg
Sampling Time: 1, 4, 24 and 72 hours post dose

Tissues/Organs	Concentration (µg equivalents/g(mL))			
	1 hr	4 hr	24 hr	72 hr
Residual Pup Carcass	ND	°0.02	0.30	0.14
Pup Oesophagus	°0.03	°0.05	°0.23	°0.07
Pup Stomach	°0.01	0.26	0.48	0.07
Milk (mL)	1.64	1.21	0.36	0.05
Plasma (mL)	13.05	6.23	0.50	0.13
Milk : Plasma ratio	0.1	0.2	0.7	0.4

ND = not detected.
° = mean includes results calculated from data below 30 d.p.m. above background.

2.6.4.9 Discussion and Conclusions

2.6.4.10 Tables and figures to include comparative TK summary

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

Table 5. Pharmacokinetics of Paricalcitol After a Single Oral or IV Dose in Rats and Dogs

Species	Dose (mcg/kg)[a]	Gender	Dose Route	$t_{½}$ (h)[b]	V_c (L/kg)	$Vd_β$ (L/kg)	CL_p (L/h•kg)	$AUC_{0-∞}$ (ng•h/mL)	C_{max} (ng/mL)	T_{max} (h)	F (%)	N
Rat	3	M	IV	2.3	0.09	0.17	0.04 (0.00)	73.76 (4.60)				4
	3	F	IV	1.2	0.10	0.18	0.04 (0.02)	34.44 (6.94)				4
	3	M	oral	2.5				12.89 (1.59)	2.79 (0.32)	1.5 (0.2)	17.5 (2.2)	4
	3	F	oral	3.0				11.16 (1.87)	2.71 (0.11)	0.8 (0.1)	32.4 (5.4)	4
	20	M	oral	1.8				43.05 (5.03)	18.02 (4.39)	1.4 (0.1)	8.8 (1.0)	4
	20	F	oral	3.2				43.82 (4.26)	19.77 (3.52)	0.8 (0.1)	19.1 (1.9)	4
Dog	0.3	M/F	IV	3.5	0.12	0.19	0.04 (0.01)	8.13 (1.42)				4
	0.3	M/F	oral	2.6				4.12 (0.29)	0.94 (0.09)	1.1 (0.2)	50.7 (3.4)	4
	1	M/F	oral	7.2				14.49 (1.81)	2.12 (0.39)	1.2 (0.2)	53.5 (0.1)	4

Data expressed as mean (SEM)

a. IV; all oral doses administered as a solution in [redacted] fractionated triglyceride of coconut oil vehicle.

b. Harmonic mean.

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

General toxicology: Repeated dose studies up to 6 months in rat and 12 months in dogs were conducted by IV administration. Paricalcitol was orally administered to rats and dogs for one month to determine that the toxicity profile was similar between the different routes. The principal effects of paricalcitol are decreased in PTH and hypercalcemia resulting from an exaggeration of the vitamin D's effect on calcium. Secondary effects of hypercalcemia included decreased food consumption, weight loss, emaciation, increased CO2, increased calcium excretion, aciduria, decreased urine specific gravity and minimal to mild renal changes.

Genetic toxicology: Paracalcitol did not exhibit genetic toxicity with or without metabolic activation in the microbial mutagenesis (Ames assay), mouse lymphoma mutagenesis assay (L5178Y) or human lymphocyte cell chromosomal aberration assay. There was no evidence of genetic toxicity in an in vivo mouse micronucleus assay.

Carcinogenicity: tested in 2-year rodent bioassays in mice and rats. In mice doses 0, 1, 3, 10 µg/kg administered SC 3X/week for 92-95 weeks in males and 102-103 weeks in females. A statistically significant increase in uterine leiomyomas and leiomyosarcomas in high dose females was observed. In rats doses of 0, 0.15, 0.5, 1.5 µg/kg was administered SC 3X/week. Mortality was increased in males treated with doses ≥0.5 µg/kg and dosing was discontinued in males in groups 0.15, 0.5, 1.5 µg/kg after weeks 98, 87, 64 respectively and male survivors were euthanized during weeks 104, 95 and 75 respectively. Surviving females were euthanized during weeks 106-108. Benign and malignant pheochromocytomas were increased in all treated males and females. The sponsor contends that the tumors were the result of chronic stimulation of chromaffin cell proliferation due to altered calcium homeostasis. Literature supports this hypothesis as

compounds causing increased calcium absorption such as sugar alcohols and vitamin D3 induce chromaffin cell proliferation and neoplasia. However calcium levels were not measured in the carcinogenicity study.

Mouse Carci	1 µg/kg		3 µg/kg		10 µg/kg	
	M	F	M	F	M	F
AUC (ng h/ml)	15.96	15.27	26.77	26.00	125.94	40.99
Exposure Multiple*	3X	3 X	5 X	5X	24X	8X

* Human AUC=5.25 ng h/ml for a 14 µg (0.24 µg/kg) dose

Rat Carci	0.15 µg/kg		0.5 µg/kg		1.5 µg/kg	
	M	F	M	F	M	F
AUC (ng h/ml)	7.56	3.12	18.75	8.57	41.79	28.39
Exposure Multiple*	1X	<1X	4X	2X	8X	5X

* Human AUC=5.25 ng h/ml for a 14 µg (0.24 µg/kg) dose
Note: previous exposure multiples were based on body surface area since human PK wasn't available.

Reproductive toxicology: Paricalcitol had no effect on male or female fertility in rats at intravenous doses up to 20 µg/kg (equivalent to 13 times the human dose of 0.24 µg/kg based on BSA. Minimal decreases in fetal viability 5% when administered daily to rabbits at doses 0.5 times the 0.24 µg/kg human dose based on BSA. At the highest dose tested (20 µg/kg 3 times per week in rats, 13 X the 0.24 µg/kg human dose based on BSA) there was a significant increase in the mortality of newborn rats at doses that caused maternal hypercalcemia.

Following a single oral administration of 20 µg/kg ^{3}H-paricalcitol to pregnant rats on GD 17 total radioactivity in the fetus revealed concentrations lower than noted in the equivalent maternal plasma sample suggesting some degree of placental transfer of parent or metabolites. Concentrations in amniotic fluid were found to be higher than noted in the fetus suggesting that total radioactivity absorbed by the fetus was being excreted.

Following single oral administration of 20 µg/kg ^{3}H-paricalcitol to lactating rats the concentrations of total radioactivity in the milk were lower than the plasma. Confirmation of pup exposure was determined by radioactivity in the pups stomach.

Special toxicology: N/A

2.6.6.2 Single-dose toxicity see NDA 20-819. No adverse effects were observed in mice and rats given 24 and 16 mg/kg respectively.

2.6.6.3 Repeat-dose toxicity

One Month Oral Toxicity in Rats (TA00-009)

Key study findings:

- **Marked decreased in PTH all doses which is related to paricalcitol pharmacologic activity**
- **Hypercalcemia at 12 and 60 µg/kg related to paricalcitol pharmacologic activity with secondary increases in CO2, aciduria and increased mineral deposition in renal tubules**
- **Minor decrease in hemoglobin, hematocrit, RBC and activated partial thromboplastin at 60 µg/kg**
- **Small increase in kidney weights both genders and liver weight of males at 60 µg/kg**
- **Single cell necrosis of renal tubular epithelial cells in 3/10 males at 60 µg/kg**

Volume #, and page #: 28.2, 001
Conducting laboratory and location: Abbott
Date of study initiation: 3/1/00 males and 3/2/00 females
GLP compliance: yes
QA report: yes (X) no ( )
Drug, lot #, and % purity: 9906ND202
Formulation/vehicle: — oil with — ethanol,
Methods :
Dosing:

Species/strain: Sprague-Dawley
#/sex/group or time point (main study):10
Satellite groups used for toxicokinetics: 5
Age: 6 weeks at treatment initiation
Weight: 123-234 g at treatment initiation
Doses in administered units: 2, 12, 60 µg/kg 3 days/week
Route, form, volume, and infusion rate: oral gavage, up to 1 ml of either 1, 6, 30 µg/ml stock solutions

Observations and times:

Clinical signs: 2x daily
Body weights:pretreatment, 2X weekly
Food consumption: pretreatment, weekly
Ophthalmoscopy: pretreatment, day 19/20
EKG: N/A
Hematology: fasted, via abdominal vein prior to necropsy
Clinical chemistry: fasted, via abdominal vein prior to necropsy
Urinalysis: fasted without water for 4 h on Day 22
Gross pathology: @ necropsy
Organs weighed: @ necropsy
Histopathology: @ necropsy
Toxicokinetics: via juglar vein, 0.5, 1, 2, 4, 8, 12, 24 h day 0, 26
Other: representative samples of liver and kidney from up to 3 male and female rats were processed for embedding after treatment for possible future ultrastructural evaluation

Results:

Mortality: one satellite rat was euthanized Day 7 with abnormal breathing sounds and ocular porphyrin staining attributed to a broken muzzle
Clinical signs: unremarkable
Body weights: unremarkable
Food consumption: unremarkable
Ophthalmoscopy: unremarkable
Hematology: HD F Decreased Hb, Hct, RBC and APTT (also HD M)

Hema-tology	0 µg/kg		2 µg/kg		12 µg/kg		60 µg/kg	
	M	F	M	F	M	F	M	F
APTT	20.41±0.48	18.4±1.08	19.83±0.72	17.45±0.8	19.36±1.52	17.75±0.63	**18.88±0.85***	**17.2±1.42***
Hb (g/dl)		15.18±0.69		14.77±0.71		14.65±0.48		**14.32±0.53***

Hct (%)		47.07±2.5		45.29±1.56		45.25±1.95		**44.19±1.69***
RBC (10E6/µl)		7.615±0.421		7.29±0.258		7.306±0.313		**7.106±0.237***

Clinical chemistry:

Clin. Chem.	0 µg/kg		2 µg/kg		12 µg/kg		60 µg/kg	
	M	F	M	F	M	F	M	F
Ca (mg/dl)	10.2±0.38	9.99±0.5	10.43±0.41	9.91±0.3	**10.84±0.57***	10.08±0.51	**12.06±0.67***	**10.76±0.4***
iCa (mmol/l)	1.173±0.042	1.214±0.048	1.098±0.073	1.11±0.076	1.104±0.128	1.186±0.058	**1.318±0.083***	**1.308±0.043***
TCO_2		24.28±1.99		**26.58±0.94***		**25.85±0.77***		**26.23±1.5***
PTH	178.76±151.35	309.08±181.19	**85.22±31.576***	**147.24±97.843***	**41.792±13.902***	**61.296±39***	**23.636±3.463***	**13.359±7.203***

Increases in ionized calcium (iCa; non-protein bound portion) are considered more biologically relevant than changes in total calcium since iCa is metabolically regulated by the parathyroid. The increases in CO_2 correspond to sustained metabolic alkalosis reported (Hulter, NH et al. (1982) Kidney International 21:445-458) with chronic administration of therapeutic agents that result in hypercalcemia (change in renal bicarbonate set point). The decreased urinary pH observed in this study is attributed to reductions in ammonia excretion based on the previous literature citation findings.

Urinalysis: MD, HD males and HD females statistically significant decrease in pH attributed to decreased ammonia excretion secondary to hypercalcemia. For HD males pH 5.6 vs. 8.22 in controls and in females 6.29 and 8 respectively.

Organ weights: increased relative kidney weight in HD attributed to increased deposition of minerals in renal tubules. Increased relative liver weight was observed in HD. In females from HD group increased relative spleen weight.

Organ Wt.	0 µg/kg		2 µg/kg		12 µg/kg		60 µg/kg	
(%body wt.)	M	F	M	F	M	F	M	F
Liver	3.046	3.129	3.077	3.121	3.138	3.042	**3.357***	3.24
Kidney	0.745	0.792	0.749	0.802	0.778	0.784	**0.81***	**0.849***
Spleen		0.2196		0.2325		0.2324		**0.2555***

Gross pathology: unremarkable

Histopathology: Mineral deposition in renal tubules was in the inner stripe and inner zone of the medulla. Both kidneys of HD groups, particularly males, contained 7-13 tubules with mineral deposits compared to 1-4 in the other groups. In 3/10 HD males there were few to occasional individual necrotic tubular epithelial cells, characterized by nuclear pyknosis within the inner medulla. The pyknotic cells did not involve tubules containing necrotic cells. Minimal to mild granular casts were noted in these individual rats which were considered treatment related.

Histopathology	0 µg/kg		2 µg/kg		12 µg/kg		60 µg/kg	
Kidney	M	F	M	F	M	F	M	F
Tubule Mineralization (min-mild; focal/multifocal)	3/10	5/10	2/10	1/10	9/10	7/10	10/10	10/10
Interstitial Inflammation	5/10	2/10	4/10	1/10	6/10	3/10	5/10	4/10
Fibrosis (focal) cortex or medulla	1/10				1/10		2/10	
Pyelonephritis diffuse, unilateral, mixed inflammatory								1/10

Liver Microgranuloma (multifocal)	5/10						7/10	
Vacuolation		2/10						4/10

Toxicokinetics:

Collection Interval	Sex	Paricalcitol Dosage (µg/kg/dose) 2	12	60
		Mean AUC_{24} (ng•hr/ml) ± SD		
Day 0	Males	13.52 ± 2.42	47.73 ± 6.00	254.38 ± 37.74
	Females	8.58 ± 2.98	32.86 ± 5.09	144.05 ± 37.21
Day 26	Males	16.22 ± 2.71	60.22 ± 7.95	220.49 ± 28.41
	Females	6.68 ± 3.04	44.56 ± 14.79	166.92 ± 38.61
		Mean C_{max} (ng/ml) ± SD		
Day 0	Males	2.969 ± 1.707	13.754 ± 1.665	81.905 ± 9.757
	Females	2.539 ± 0.584	9.725 ± 2.431	63.215 ± 16.437
Day 26	Males	2.508 ± 0.659	14.527 ± 1.848	62.353 ± 11.816
	Females	1.931 ± 1.044	14.057 ± 4.193	54.145 ± 15.440

TK is dose proportional, similar exposure Day 0 vs. Day 26, AUC higher in males than females.

Summary of individual study findings: Identification of the kidney as the target organ is consistent with findings found via the intravenous route. As expected, exposures were higher via the intravenous route (e.g. 3 month IV rat 3 µg/kg AUC_{males}=84.33±8.3 ng h/ml and $AUC_{females}$=40.2±13 ng h/ml). The renal mineralization and inflammation appear related to hypercalcemia as a function of exaggerated pharmacologic activity of paricalcitol. Liver microgranuloma and vacuolization is seen at HD although these findings were not associated with perturbations in liver enzymes. The sponsor suggests a NOTEL=60 µg/kg however based on the kidney histopathology and hematology findings at this dose the NOAEL=12 µg/kg (40-60 ng h/ml or ≥7X the human IV MRHD of 0.24 µg/kg where AUC=5.5 ng h/ml). There are elevations in calcium and PTH at the NOAEL which are attributed to the pharmacologic effect of the paricalcitol on normal healthy animals. These findings would be closely monitored in clinical trials as they represent clinical efficacy endpoints for this indication.

One Month Oral Toxicity in Dogs (TB00-010)

Key study findings:

- **Marked decreases in PTH**
- **Hypercalcemia**
- **Secondary effects of hypercalcemia: decreased food consumption, weight loss and emaciation, increased total CO_2 increased fractional excretion of calcium, aciduria, decreased urine specific gravity, multifocal minimal-mild cortical tubular dilation with decreased epithelium, multifocal minimal degeneration (sloughing/necrosis) tubular epithelium, multifocal minimal tubular epithelial regeneration (basophilic, hypercellular) and multifocal minimal to mild interstitial lymphoplasmacytic inflammatory infiltrates**

Volume #, and page #: 28.1 pg. 001
Conducting laboratory and location: Abbott; Abbott Park, IL
Date of study initiation: 2/23/00 male treatment; 2/24/00 female treatment
GLP compliance: yes

QA report: yes (x) no ( )
Drug, lot #, radiolabel. and % purity: 9906ND202
Formulation/vehicle: [redacted] oil with [redacted] ethanol 0.1 ml/kg of stock formulations (0, 5, 8, 12 µg/ml) were placed in gelatin capsules for administration

Methods :
Dosing:

Species/strain: beagle dog
#/sex/group or time point (main study): 3
Satellite groups used for toxicokinetics or recovery: 0
Age:7 months
Weight: 8.07-9.78 kg at treatment initiation
Doses in administered units: 0, 0.5, 0.8, 1.2 µg/kg @ 3X weekly
Route, form, volume, and infusion rate: oral, capsule, 0.1 ml/kg

Observations and times:

Clinical signs: 2X daily
Body weights: pretreatment, 2X weekly
Food consumption: 2X weekly
Ophthalmoscopy: pretreatment, end of treatment
EKG: pretreatment, end of treatment
Hematology: 0.5, 1, 2, 4, 8, 12, 24 h post dose day 0, 21 via juglar vein
Clinical chemistry: fasted pretreatment, day 27 also day 6 for BUN, creat, Ca, iCa, ALP, Alb, PTH and Days 13 & 20 for Ca, iCa and Alb
Urinalysis: from bladder at ncecropsy
Toxicokinetics: 0.5, 1, 2, 4, 8, 12, 24 h post dose day 0, 21
Other: representative liver and kidney from all dogs were embedded for possible future ultrastructural evaluation

Results:

Mortality: none

Clinical signs: 1/3 HD females had slight emaciation beginning Day 12 which progressed to moderate over the study. Males, 2/3 at MD had slight emaciation beginning Days 16 and 23 respectively. Anorexia appeared to be the cause of the emaciation.

Body weights: Among males, 2/3 MD lost 11-19% of the initial body weight by the end of treatment but no statistically significant differences in mean body weight or mean weight changes. Among females, 1/5 MD and 2/3 HD lost 9-11% of their initial weight. Mean body weight changes for these females were statistically significantly lower than for controls and on occasional days mean weight values for one or both MD, HD were statistically significantly lower than the respective control. The greatest weight loss (>1 kg) occurred in the 3 dogs which appeared emaciated.

Food consumption: Marked decreases were observed in 3 dogs that appeared emaciated and lost >1 kg body weight. Anorexia was apparent during the second week of dosing for HD and during week 3-4 for the MD group. These animals were fed a diet slurry of ground feed beginning on Days 14 and 16 respectively. Anorexia has been noted with hypercalcemia.

Ophthalmoscopy: reported as unremarkable
Electrocardiography: reported as unremarkable

Hematology	0 µg/kg		0.5		0.8		1.2	
Day 27	M	F	M	F	M	F	M	F
APTT 9sec)	13.63± 0.57	14.07± 0.12	14.37± 0.15	14.57± 0.49	14.83± 1.29	14.6± 0.4	14.73± 0.21	14.97± 0.4*

Clinical chemistry:

		Mean Serum Total Calcium Concentration (mg/dl)				
		Pretest	Day 6	Day 13	Day 20	Day 27
T_0	0 µg/kg/dose	10.73/10.87[a]	11.00/11.13	11.03/11.37	11.47/10.70	10.93/10.93
T_1	0.5 µg/kg/dose	10.70/11.27	12.67/12.57	12.10/11.83	13.53/12.17	13.60/13.37
T_2	0.8 µg/kg/dose	11.10/11.10	14.37/13.90	14.23/13.17	14.63/13.20	14.30/13.37
T_3	1.2 µg/kg/dose	10.67/10.63	14.57/14.60	13.83/14.10	15.27/13.57	14.83/13.93

a. Males/Females

		Mean Serum Ionized Calcium Concentration (mmol/l)				
		Pretest	Day 6	Day 13	Day 20	Day 27
T_0	0 µg/kg/dose	1.340/1.397[a]	1.390/1.380	1.343/1.367	1.347/1.377	1.370/1.333
T_1	0.5 µg/kg/dose	1.360/1.393	1.483/1.377	1.480/1.500	1.597/1.613	1.690/1.620
T_2	0.8 µg/kg/dose	1.383/1.407	1.627/1.573	1.583/1.537	1.777/1.700	1.930/1.687
T_3	1.2 µg/kg/dose	1.360/1.403	1.580/1.700	1.567/1.707	1.813/1.740	1.900/1.657

a. Males/Females

Clin Chem	0 µg/kg		0.5 µg/kg		0.8 µg/kg		1.2 µg/kg	
Day 27	M	F	M	F	M	F	M	F
BUN (mg/dl)	13.3±1.2		19.7±7.2		21.7±3.1*		19±3.6	
Cl (mmol/l)	116.3±2.3	111.3±0.6	114.3±1.5	111.3±0.6	112.3±1.2	108.7±1.2*	112±2	109±1*
Bile (µmol/l)	2.37±0.42	2.97±0.47	3.83±0.9	4.47±1.34	5.8±3.56*	8.1±2.33*	5.73±2.08*	6.73±1.81*
ALP (IU/l)	111±5	97.7±21.5	102±5	81.7±9.5	89.3±8.4	130.3±32.6	77.7±15.6*	105.3±21
TCO_2 (mmol/l)	24.23±1.33	25±0.78	26.67±2.12	25.63±1.19	28.63±0.55*	29.3±0.17*	28.1±0.7*	27.8±0.89*
Na (mmol/l)		147.7±0.6		147.7±0.6		147.7±0.6		146±1*
PTH (pg/ml)	28.203±8.92	30.747±16.698*	1.547±0.257*	1.78±0.338*	1.623±0.393*	1.337±0.257*	1.687±0.949*	1.59±0.239*

Urinalysis: Mean specific gravity for the HD males and all groups of treated females were statistically significantly lower than controls by study end. Mean values from LD and MD males were lower than controls but not statistically significantly lower. Deficient urine concentrating ability (evident from statistically significant decreased fractional Ca excretion in all treated groups) relates to the hypercalcemia which usually precedes increases in BUN and serum creatinine. Clearly impaired renal clearance of calcium is apparent from clinical chemistry and renal histopathology. Although LD, MD males had statistically significant increases in BUN the means were minimally increased and creatinine was not elevated suggesting that renal function was not significantly impaired.

Urine pH means of treated females were statistically significantly lower than controls. Aciduria has been observed with cacitriol treatment of dogs and attributed to an increase in plasma bicarbonate set point of the kidney.

Organ weights: Statistically significant increased relative (%BW) pituitary weight in MD (0.0007%) and HD (0.0008%) males relative to control (0.0005%). Females were unremarkable.

Gross pathology: unremarkable

Histopathology: Findings attributed to hypercalcemia and concurrent segmental ischemia

- Multifocal, minimal-mild cortical tubular dilation and decreased epithelium lining
- Multifocal minimal degeneration (sloughing/necrosis) of tubular epithelium
- Multifocal, minimal tubular epithelial regeneration (basophilic, hypercellular)
- Multifocal, minimal-mild interstitial lymphoplasmacytic inflammatory infiltrates
- Scattered foci of mineralization in the medulla in control and drug treated animals however 10/18 drug treated animals had minimal cortical intratubular mineralization with minimal to mild severity in LD, MD and slightly greater severity in HD group animals

Histopath	0 µg/kg		0.5 µg/kg		0.8 µg/kg		1.2 µg/kg	
Kidney tubular	M	F	M	F	M	F	M	F
Multifocal regeneration			2/3		3/3		3/3	
Multifocal degeneration			2/3	2/3	3/3	3/3	3/3	2/3
Multifocal mineralization	3/3		3/3		3/3		3/3	
Inflammation			3/3	3/3	3/3	3/3	3/3	3/3 1/3 mixed inflam. infiltrate
Dilation			1/3	3/3	3/3	2/3	3/3	3/3

Toxicokinetics: The approved injectable dose is 0.24 mg/kg corresponding to an AUC=5.5 ng h/ml. Human PK for the capsule formulation has not been provided.

Collection Interval	Sex	Paricalcitol Dosage (µg/kg/dose) 0.5	0.8	1.2
		Mean AUC_{24} (ng•hr/ml) ± SD		
Day 0	Males	3.68 ± 0.51	7.41 ± 1.11	8.31 ± 1.82
	Females	3.79 ± 0.46	6.60 ± 2.14	7.23 ± 2.07
Day 21	Males	3.72 ± 0.62	4.96 ± 1.76	6.36 ± 1.80
	Females	3.73 ± 0.43	4.92 ± 1.55	5.99 ± 1.32
		Mean C_{max} (ng/ml) ± SD		
Day 0	Males	0.754 ± 0.072	1.603 ± 0.211	1.606 ± 0.359
	Females	0.869 ± 0.173	1.568 ± 0.717	1.470 ± 0.559
Day 21	Males	0.884 ± 0.269	1.333 ± 0.301	1.537 ± 0.345
	Females	0.809 ± 0.212	1.358 ± 0.334	1.493 ± 0.226

No gender related differences were observed unlike the rat, increases in PK were approximately dose proportional.

Summary of individual study findings: Decreases in PTH and hypercalcemia are related to the pharmacologic activity of paracalcitol. The renal tubular dilation, degeneration, epithelial regeneration and interstitial lymphoplasmacytic inflammatory infiltrates, anorexia, weight loss, increased total CO2,

increased fractional excretion of calcium, aciduria, and decreased urinary specific gravity are related to the hypercalcemia. The sponsor dismisses these effects as toxicologically insignificant and reports a NOTEL=1.2 μg/kg. Although these findings relate to the pharmacologic effect of paricalcitol they are still adverse effects. Therefore a NOAEL< 0.5 μg/kg is reasonable based on the observed kidney findings. The renal tubular histopathology observed in virtually all treated animals occurs with a similar incidence in the 3 month IV dog study at lower doses (0.1, 0.3 μg/kg where AUC=6 ng h/ml).

Toxicology summary: The kidney is the target organ of toxicity in both the rat and dog. The renal tubular histopathology findings are related to the hypercalcemia (and decreased PTH) which is an extension of the pharmacologic activity of paricalcitol. Based on these findings a NOAEL= 12 μg/kg (44-60 ng h/ml) was established in the one-month rat oral gavage toxicity study. Dosing intervals used in toxicity studies were three times weekly since excessive pharmacologic activity would have prevented daily dosing at comparable exposures. Liver microgranuloma and vacuolization were seen in rats given 60 μg/kg in the absence of clinical chemistry correlates. Decreased hemoglobin, hematocrit and RBC were decreased in rats given 60 μg/kg. The hypercalcemia and decreased PTH along with the resulting renal tubular histopathology were also observed in the one month oral (capsule) study in dog. A NOAEL <0.5 μg/kg (<3.7 ng h/ml) was established. Anorexia, weight loss, increased TCO2, increased fractional excretion of calcium, aciduria and decreased urinary specific gravity were seen in the dog and attributed to hypercalcemia.

Toxicology conclusions: Hypercalcemia, reduced PTH and the ensuing renal tubular histopathology were observed in both rat and dog following one month treatment with paricalcitol. These findings using an oral route (gavage for rat and capsule for dog) are consistent with those observed in previous studies using an intravenous route. No expected toxicity is observed with oral compared to IV administered drug (NDA 20-819).

Histopathology Inventory for IND #60, 672

Study	1 Mo.	1 Mo
Species	Rat	Dog
Adrenals	x*	x*
Aorta	x	x
Bone Marrow smear	x	x
Bone (femur)	x	
Brain	x *	x*
Cecum	x	
Cervix		
Colon	x	x
Duodenum	x	x
Epididymis	X*	X*
Esophagus	x	x
Eye	x	x
Fallopian tube		
Gall bladder		x
Gross lesions	x	x
Harderian gland		
Heart	x *	x*
Ileum	x	x
Injection site		
Jejunum	x	x
Kidneys	x *	x*
Lachrymal gland		
Larynx		
Liver	x *	x*
Lungs	x	
Lymph nodes, cervical	x	x
Lymph nodes thoracic	x	x
Lymph nodes, mesenteric	x	x
Mammary Gland	x	x
Nasal cavity		
Optic nerves		
Ovaries	x *	x*
Pancreas	x	x
Parathyroid	x *	x*
Peripheral nerve		
Pharynx		
Pituitary	x *	x*
Prostate	x *	x*
Rectum		
Salivary gland	x	x
Sciatic nerve	x	x
Seminal vesicles	x	x*
Skeletal muscle	x	x
Skin	x	x
Spinal cord	x	x
Spleen	x *	x*
Sternum		
Stomach	x	x

Testes	x *	x*
Thymus	x *	x
Thyroid	x *	x*
Tongue		
Trachea	x	x
Urinary bladder	x	x
Uterus	x *	x*
Vagina	x	x
Zymbal gland		
Standard List		
Bone (rib)		x

X, histopathology performed
*, organ weight obtained

2.6.6.4 Genetic toxicology see NDA 20-819
2.6.6.5 Carcinogenicity see NDA 20-819
2.6.6.6 Reproductive and developmental toxicology see NDA 20-819
2.6.6.7 Local tolerance see NDA 20-819
2.6.6.8 Special toxicology studies see NDA 20-819

2.6.7 TOXICOLOGY TABULATED SUMMARY

Table 6. Repeated-Dose Toxicity Studies Conducted Using IV and Oral Administration of Paricalcitol

Species	Strain, Supplier	Duration (Months)	Dosages (mcg/kg/day)	NTED	AUC (ng•hr/ml) ± SD)	Target Organs
IV Studies						
Rat	CD® (SD)BR	1 (2-week recovery)	0, 0.3, 3.0, 20.0	0.3[a]	ND	Kidney, stomach, aorta, heart
Rat	CD® (SD)BR	3	0, 0.1, 0.5,3.0	3.0	M 84.3 ± 8.3 F 40.2 ± 13.0	Kidney
Rat	CD® (SD)BR	6	0, 0.1, 0.5, 3.0	0.5	M 14.6 ± 1.5 F 6.9 ± 1.1	Kidney, heart, urinary bladder, bone
Dog	Beagle	1 (2-week recovery)	0, 0.1, 0.3, 0.6, 1.0	0.1	M 1.3 ± 0.4 F 1.5 ± 0.9	Kidney, aorta, liver thymus, parathyroid
Dog	Beagle	3	0, 0.02, 0.1, 0.3	0.02	M 0.7 ± 1.4 F 0.5 ± 0.6	Kidney, aorta, thymus, parathyroid, testis, prostate
Dog	Beagle	6	0, 0.02, 0.06, 0.2	0.06	ND	Kidney, aorta, thymus, parathyroid
Dog	Beagle	12	0, 0.02, 0.06, 0.2	0.02	M 0.9 ± 1.1 F 0.5 ± 0.4	Kidney, pulmonary artery, stomach, parathyroid
Oral Administration Studies						
Rat	CD® (SD)BR	1	0, 2, 12, 60	60[a]	M 254 ± 38 F 144 ± 37	Kidney
Dog	Beagle	1	0, 0.5, 0.8, 1.2	1.2	M 8.3 ± 1.8 F 7.2 ± 2.1	Kidney

a. Study conducted using high calcium (normal) rat chow
ND = Not determined

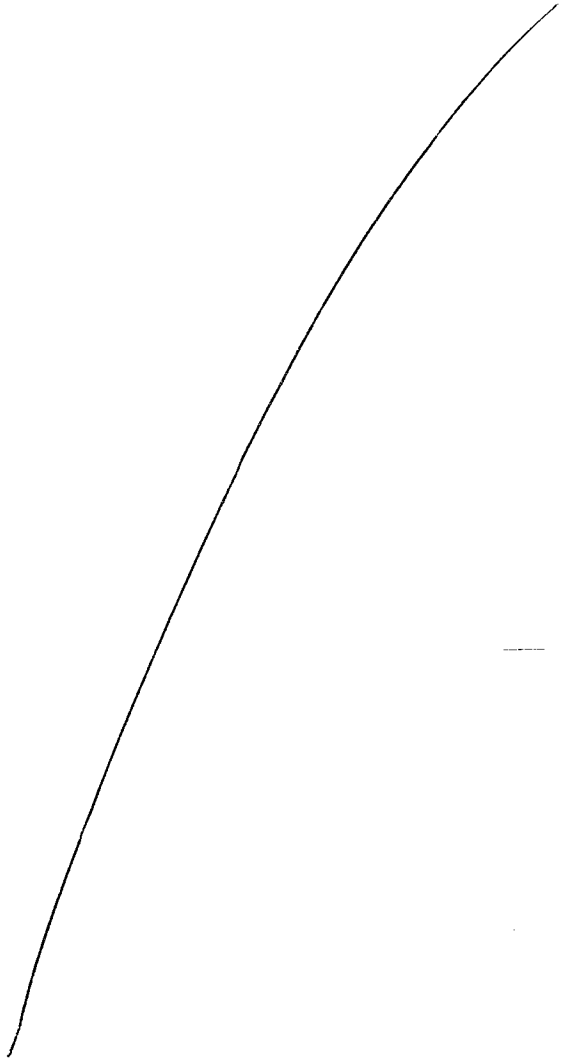
OVERALL CONCLUSIONS AND RECOMMENDATIONS

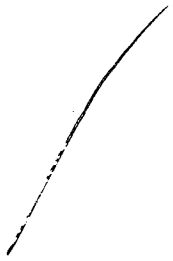
Conclusions: The toxicology findings via oral administration in rat and dog are consistent with the previously approved Zemplar NDA 20-819 for an IV formulation.

Unresolved toxicology issues (if any): none

Recommendations: approval pending labeling changes

Suggested labeling: According to the sponsor, patients with CKD show similar exposures to healthy volunteers therefore a 14 μg dose (0.24 μg/kg) results in an AUC=5.25 ng h/ml.





APPENDIX/ATTACHMENTS N/A

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Karen Davis-Bruno
2/4/05 04:23:49 PM
PHARMACOLOGIST