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APPLICATION NUMBER: 020862

PHARMACOLOGY REVIEW(S)

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NDA 20-862 June 7, 1999

DRUG: 1α-OH-Vitamin D_2 (Hectorol)

INDICATION: Secondary hyperparathyroidism (HPT) of renal failure

TEAM LEADER MEMO TO FILE REGARDING PRECLINICAL PHARMACOLOGY/TOXICOLOGY DISCUSSION OF PREGNANCY CATEGORY DETERMINATION FOR NDA 20-862 (1α-OH-Vitamin D_2, Hectorol)

In the initial sponsor proposed label, there was no pregnancy category listed. In the initial pharmacology review, it was proposed that Hectorol receive a category C based on the following findings in the reproductive toxicology studies in rabbits:

1. Minimal reduction in fetal weights and slightly increased incidence in late resorptions at doses of 0.1 µg/kg/day.
2. Slight increases in number of litters with unossified sternebrae and rib cartilage variations at 0.3 µg/kg/day.

Note that there were no specific findings of teratogencity.

Other related products (rocaltrol and paracalcitrol) have category C listings which include findings of teratogenicity and neonatal death in addition to late resorptions. The relative levels of human exposure in the Hectorol experiments were lower than those used in the other two products, but it was determined in discussions including Gemma Kuijpers (reviewer), C. Joseph Sun, (associate director for pharmacology/toxicology ODEII) and myself (pharmacology team leader, DMEDP) that the maternal weight loss that occurred at the high dose of 0.3 µg/kg/day with Hectorol was excessive and that the findings in this group were not relevant to human exposure. Therefore, in consideration of the findings at the mid dose group of 0.1 µg/kg/day, it was decided that a category B listing was more appropriate. The proposed final labeling incorporating this decision is provided below:

Carcinogenesis, Mutagenesis, Impairment of Fertility

DRAFT LABELING

[redacted]

Use in Pregnancy

DRAFT LABELING

[redacted]

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DRAFT LABELING [redacted]

Data supporting the decision to base the labeling on the mid dose (1µg/kg/day) group are provided in the following tables. Note that hypercalcemia and body weight loss are noted in the mid dose group without accompanying fetal effects. The weight loss in the high dose 0.3µg/kg/day) females was considered excessive and thus, the findings are not relevant to human exposure. Weight loss in the mid dose group is also excessive, but no significant reproductive findings were noted. It appears that rabbits are very sensitive to Hectorol and it was not possible to test at significant multiples of human exposure in this species.

Body weight effects in rabbits treated with hectorol during Gestation (grams)

Group (mcg/kg)	Body weight gain			Body weight (Day 29)
	Day 0-6	Day 6-19	Day 19-29	
controls	91	295	183	100%
0.03	98	201*	168	97%
0.1	69	-24*	307*	95%*
0.3	102	-192*	393*	93%*

*statistically significant

Resorption and serum Ca in affected animals in rabbit study with Hectorol

Group	# animals	#resorptions	#animals with resorptions	Ca (mean of whole group)	Ca (mean of animals with resorption)
Control	19	3	3	12.43	12.20
LD	19	2	2	12.28	12.27
MD	19	3	3	12.62	13.29
HD	20	9	8	13.11	13.13

This information was forwarded to Joe Sun, associate director of pharmacology/toxicology for ODEII and Leah Ripper. No further action is indicated at this time.

/s/ [redacted] 6/7/99

Ronald W. Steigerwalt, Ph.D.
Pharmacology Team Leader

cc: NDA Arch
HFD510
HFD510/Steigerwalt/Kuijpers/Hedin
HFD570
Review Code: AP
Filename: 20862.tlmem.doc

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HECTOROL NDA REVIEW
PHARMACOLOGY/TOXICOLOGY

FEB 16 1999

NDA:	20,862
Submission date:	March 7, 1998
Review date:	February 5, 1999
Drug:	1α-OH-Vitamin D_2
Drug name:	Hectorol (TSA-870) (BCI-101)
Drug category:	Vitamin D analog (Hormone)
Indication:	Secondary hyperparathyroidism (HPT) of renal failure.
Clinical dose:	Initially, 10 µg 3x/week. Adjust dose to control HPT.
Maximum dose:	60 µg/week
Dose formulation:	Soft gelatin capsule, 2.5 µg
Sponsor:	Bone Care International One Science Court Madison, WI 53711
Related Submissions:	IND [redacted] IND IND
Medical Officer:	L. Lutwak
Chemist:	M. Haber
Pharmacologists:	D. Coleman, G. Kuijpers
Biopharmaceutics:	R. Kavanagh
C. S. O.:	R. Hedin
Recommendation:	AP (pending labeling)

/S/ [redacted]

Gemma Kuijpers, Ph.D.
Pharmacologist.

Concur /S/ [redacted] 2/16/99

Ron Steigerwalt, Ph.D.
Team Leader, Pharmacology.

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	1. IND [redacted]	
	2. IND	
	3. IND	
	4. IND	
	5. IND	
	6. IND	

Note: There are no carcinogenicity or bone quality studies with Hectorol.

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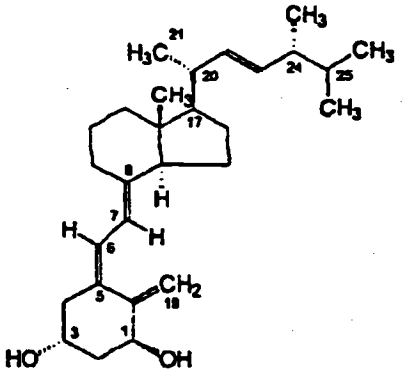
INTRODUCTION

The compound Hectorol (1α(OH)-Vitamin D_2, or, 1a-OH-D2) is a synthetic vitamin D_2 analog
It is converted to the active metabolite, 1a-OH, 25-OH-D2 by C-25-hydroxylation in the liver, and unlike vitamin D2 absorbed in the diet, it does not need to be 1a-hydroxylated in the kidney.

Structure:



Molecular formula: $C_{28}H_{44}O_2$

Molecular weight (calculated): 412.66

The effect of the calciotropic hormones vitamin D2 and D3, i.e., of the active hydroxylated metabolites, is to stimulate Ca uptake from gut, increase serum Ca and thereby inhibit PTH release. Also, vitamin D directly inhibits PTH synthesis by the parathyroid, and it reduces renal Ca excretion. It follows that the expected toxicity of vitamin D analogs is hypercalcemia and tissue mineralization.

In secondary hyperparathyroidism (HPT) due to renal failure there is an increase in PTH secretion that is adaptive and not due to parathyroid gland dysfunction. Renal failure is associated with decreased GFR, thus an increase in serum P, a decrease in serum Ca and a compensatory increase in PTH secretion. Increased PTH mobilizes Ca from bone and inhibits P reabsorption in renal tubules. Hyperphosphatemia can also inhibit renal production of 1,25(OH)2D3 exacerbating hypocalcemia. Administration of vitamin D or an analogue will counteract the physiological changes in Ca and P metabolism and increased PTH status due to renal failure.

Treatment of secondary HPT and its associated bone disease, renal osteodystrophy, depends on the stage of the disease. Currently, dietary restriction of phosphate, dietary phosphate binders, calcium supplementation, hemodialysis, and/or vitamin D therapy, is used. Vitamin D can be given as vitamin D2 (ergocalciferol) supplement, calcitriol (Calcijex,i.v., or Rocaltrol, oral), or a vitamin D analogue such as paracalcitol (Zemplar, oral).

The proposed human dose (oral) of Hectorol is 10 μg (approximately 0.17 ug/kg), first 3 times a week, then adjust the dose to control HPT. The maximal dose used in trials was 60 ug/week.

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ANIMAL TOXICITY STUDIES

I	Acute Toxicity Study in Mice (Oral and IP) [redacted]14-88)
II	Acute Oral Toxicity Study in Rats [redacted]615-001)
III	Acute IP Toxicity study in Rats [redacted]-14-82)
IV	Four Week Oral Comparative Toxicity Study of 1-OH-D2 and 1-OH-D3 in Rats [redacted]14-90)
V	13- Week Oral Toxicity Study in Rats (Summary, see attached complete review)
VI	One year Oral Toxicity Study in Rats (Summary, see attached complete review)
VII	Two- Week Oral Toxicity Study in Cynomolgus Monkeys (Summary, see attached complete review)
VIII	13-Week Oral Toxicity Study in Cynomolgus Monkeys (Summary, see attached complete review)
IX	One year Oral Toxicity Study in Cynomolgus Monkeys (Summary, see attached complete review)
X	Overall Summary and Conclusions of Toxicity Studies.

Acute Toxicity Study in Mice (Oral and IP) ([redacted]14-88)

PURPOSE:

To assess the acute toxicity and LD-50 of Hectorol in mice when administered orally or IP.

EXPERIMENTAL DESIGN:

Testing Facility: [redacted]
Study #: [redacted]14-88
Study Initiated: 11/28/91
Study Completed: 4/10/92
Dose & Formulation: 0, 160, 320, 630, 1250 ug/kg oral.
0, 3.8, 7.5, 15, 30, 60, ug/kg IP injection.
Gavage or IP single dose, in 2 ml of coconut oil.
Batch of drug: lot Ecl α OH927904, crystalline form
Food: Commercial rodent chow, CE-2, [redacted]
GLP statement: Included and signed.
Animals: Jcl:ICR mice were purchased from [redacted] 4 weeks old, 19-25 g.

Group	Dose (ug/kg)	# of Animals
ORAL:		
0	0	5 males + 5 Females
1	160	5 males + 5 Females
2	320	5 Males + 5 Females
3	630	5 males + 5 Females
4	1250	5 males + 5 Females
I.P.		
0	0	5 males + 5 Females
1	3.8	5 males + 5 Females
2	7.5	5 males + 5 Females
3	15	5 Males + 5 Females
4	30	5 males + 5 Females
5	60	5 males + 4 Females

Mice were fasted for 5 hours before dosing and observed for 21 days after dosing.

RESULTS:

OBSERVED EFFECTS:

Group:	Dose (ug/kg):	# of Animals and finding:
ORAL:		
0	0	None
1	160	None
2	320	3 m, 3 f: Transiently, reduced motility, dyspnea, hyporeactivity, ataxia, abdominal position, and emaciation.
3	630	All animals: Transiently reduced motility, dyspnea, ataxia, abdominal position, ptosis and emaciation. 2 females: Transient eye discharge. Sustained hyporeactivity and reduced motility in females.
4	1250	All animals: Reduced motility, dyspnea, ataxia, abdominal position, ptosis and emaciation, eye discharge, hyporeactivity and reduced motility persisted until death.
I.P.		
0	0	None
1	3.8	None
2	7.5	None
3	15	Decreased defecation from day 3-10.
4	30	2 m, 2 f: Transiently reduced motility, dyspnea, ataxia, and abdominal position. 2 females: transient ptosis. All animals: transient emaciation.
5	60	All animals: Reduced motility, dyspnea, ataxia, abdominal position, ptosis and emaciation, eye discharge, hyporeactivity and reduced motility persisted until death

MORTALITY:

Group:	Dose (ug/kg):	# of Deaths:
ORAL:		
0	0	None
1	160	None
2	320	1 male on day 2.
3	630	4 males and 4 females died on days 3-7.
4	1250	All 5 males and 5 females died on days 3-6.
I.P.		
0	0	None
1	3.8	None
2	7.5	None
3	15	None
4	30	1 male on day 6.
5	60	All 5 males and 5 females died on days 3-6.

BODY WEIGHT:

Group:	Dose (ug/kg):	Finding:
ORAL:		
0	0	None
1	160	None
2	320	Transient 10% weight loss, normal weight gains thereafter.
3	630	Transient 15% weight loss, normal weight gains thereafter.
4	1250	~ 15% weight loss, all animals died by day 6.
I.P.		
0	0	None
1	3.8	None
2	7.5	None

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3	15	Transient 10% weight loss, normal weight gains thereafter.
4	30	Transient 15% weight loss, normal weight gains thereafter.
5	60	~ 15% weight loss, all animals died by day 6.

FOOD CONSUMPTION: Not determined.
EYE EXAMINATION: Not determined.
HEMATOLOGY and COAGULATION: Not determined.
BLOOD CHEMISTRY: Not determined.
URINALYSIS: Not determined.
ORGAN WEIGHTS: Not determined.

NECROPSY FINDINGS:

Group: ORAL:	Dose (ug/kg):	Finding (number and severity of incidence not provided)
0	0	None
1	160	None
2	320	Small thymus and spleen, pale liver and kidney, tan foci on heart.
3	630	Small thymus and spleen, pale kidney, and tan foci on heart.
4	1250	Deceased animals (all doses) had lung congestion, pale kidneys and small spleens.
I.P.		
0	0	None.
1	3.8	None.
2	7.5	Pale kidneys.
3	15	Pale kidneys.
4	30	Tan foci on the heart and pale kidneys.
5	60	Lung congestion and small spleens in the deceased animals at all doses.

GROSS and HISTOPATHOLOGY:
Not determined except as noted above for necropsy findings.

SUMMARY and CONCLUSIONS:

Common dose dependent findings were reduced motility, dyspnea, hyporeactivity, ataxia, abdominal position, reduced defecation and body weight, tan foci on the hearts of surviving animals and renal discoloration and small spleens on the deceased animals. These toxicities reflect the pharmacological effect of the drug to cause hypercalcemia.

Route:	Minimal lethal dose (ug/kg)	HED* (ug/kg) based on mg/m² comparison	LD-50 (ug/kg)	HED* (ug/kg)	Human dose multiple**
P. O. males	320	26	449	37	222 x
P. O. females	630	52	495	41	246 x
I. P. males	30	2.5	35	3	19 x
I. P. females	60	5	30-60	2.5-5	16 – 30 x

*** HED = human equivalent dose**
**** Assume human dose of 10 ug**

Males appear to be slightly more sensitive to the drug. The minimum lethal dose and the LD-50 are very close together indicating a very steep toxicity curve. However, this LD-50 (P.O.) is ~250-times the proposed human oral dose (10 µg), when doses are compared on a mg/m² body surface area basis. The validity of this dose comparison is discussed in the ADME section of this review.

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Acute Oral Toxicity Study in Rats. ([redacted] 615-001)

PURPOSE:

To assess the acute toxicity and LD-50 of Hectorol in rats when administered orally.

EXPERIMENTAL DESIGN:

Testing Facility: [redacted]
Study #: 615-001
Study Initiated: 3/14/89
Study Completed: 12/27/89
Dose & Formulation: 0, 1.25, 2.5, 5, 10 mg/kg oral.
Gavage single dose, in 2 ml/kg of coconut oil.
Batch of drug: lot 2, solution prepared by the sponsor.
Food: Purina certified rodent chow # 5002.
GLP statement: Included and signed.
Animals: Charles River CD Rats were 8-10 weeks old, m:213-290g f:163-203 g.

Group:	Dose (mg/kg):	# of Animals:
ORAL:		
0	0	5 males + 5 Females
1	1.25	5 males + 5 Females
2	2.5	5 Males + 5 Females
3	5	5 males + 5 Females
4	10	5 males + 5 Females

Rats were fasted for 18-19 hours before dosing and observed for 15 days after dosing.

Dose Selection: No rationale provided.

RESULTS:

OBSERVED EFFECTS:

Group:	Dose (mg/kg):	# of Animals and finding
0	0	None
1	1.25	Four animals had decreased activity on days 4-7. Three animals had discolored material or staining around the mouth on days 4-7.
2	2.5	3 soft stool or diarrhea. 4 decreased activity on days 4-7. Three animals had discolored material or staining around the mouth on days 4-7.
3	5	3 soft stool or diarrhea. 4 decreased activity on days 2-4.
4	10	3 soft stool or diarrhea. 4 decreased activity on days 2-4.

MORTALITY:

Group:	Dose (mg/kg):	# of Deaths
0	0	None
1	1.25	2 males died on day 4.
2	2.5	2 males and 4 females died on day 4, 1 male and 1 female died on day 5.
3	5	5 males died on days 3-4. 5 females died on days 4-5.
4	10	All 5 males died on day 4. 5 females died on days 4-5.

BODY WEIGHT:

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Group:	Dose (mg/kg):	Finding
0	0	None
1	1.25	Transient 10% weight loss (day 8), return to normal (day 15).
2	2.5	Transient 20% weight loss (day 8), 2 surviving males were normal on day 15.
3	5	No animals survived to weigh in on day 8.
4	10	No animals survived to weigh in on day 8.

FOOD CONSUMPTION: Not determined.
EYE EXAMINATION: Not determined.
HEMATOLOGY: Not determined.
COAGULATION: Not determined.
BLOOD CHEMISTRY: Not determined.
URINALYSIS: Not determined.
ORGAN WEIGHTS: Not determined.

NECROPSY FINDINGS:

Group:	Dose (ug/kg):	# of Animals and finding:
0	0	None
1	1.25	9/10 had foci and congestion of the stomach mucosa, 3 m had tan foci on the hearts and 1 male had red foci on the kidneys. 1 deceased male had congestion of the lungs.
2	2.5	10/10 had foci and congestion of the stomach mucosa, 8/10 tan foci on the hearts and 5/10 red foci on the kidneys. 5/8 Deceased had congestion of the lungs.
3	5	10/10 had foci and congestion of the stomach mucosa, only 2 males had red foci on the kidneys and none had tan foci on the hearts perhaps because they died too soon to show evidence of calcification.
4	10	10/10 had foci and congestion of the stomach mucosa, only 2 females had red foci on the kidneys but almost all animals had tan foci on the hearts and staining around the nose and anus.

GROSS and HISTOPATHOLOGY: Not determined except as noted above for necropsy findings.

SUMMARY and CONCLUSIONS:

Common dose dependent findings were weight loss, diarrhea, reduced activity, foci and congestion of the stomach mucosa, tan foci on the hearts and red foci on the kidneys of surviving animals and congestion of the lungs and staining around the mouth and anus of the deceased animals. These toxicities most likely reflect the pharmacological effect of the drug to cause hypercalcemia.

Route:	Minimal lethal dose (ug/kg)	HED* (ug/kg) based on mg/m^2 comparison	LD-50 (ug/kg)	HED* (ug/kg)	Human dose multiple**
P. O. males	1250	208	1700	283	1700 x
P. O. females	2500	416	1800	300	1800 x

* HED = human equivalent dose
** Assume human dose of 10 ug

Males appear to be slightly more sensitive to the drug, dying sooner and at slightly lower doses. The minimum lethal dose and the LD-50 are very close together indicating a very steep toxicity curve. However, this LD-50 (P.O.) is ~1800-times the proposed human oral dose (10 µg) when doses are compared on a mg/m^2 basis. The validity of this comparison is discussed in the ADME section of this

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review.

Acute IP Study of [redacted]870 Toxicity in Rats ([redacted]14-82)

PURPOSE:

To assess the acute toxicity and LD-50 of Hectorol in rats when administered IP.

EXPERIMENTAL DESIGN:

Testing Facility: [redacted]
Study #: [redacted]14-82
Study Initiated: 11/28/91
Study Completed: 3/27/92
Dose & Formulation: 0, 17, 33, 65, 130, 250 ug/kg IP single dose, in 2 ml of coconut oil. Rats were dosed once, observed for 21 days and surviving rats were sacrificed.
Batch of drug: lot Ecl α OH927904, crystalline form
Food: Commercial rodent chow, CE-2, [redacted] Rats were allowed free access to food and tap water.
GLP statement: Included and signed.
Animals: Jcl:ICR mice were purchased from [redacted], 4 weeks old, 19-25 g.

Group	Dose (ug/kg)	# of Animals
I.P.		
0	0	5 males + 5 Females
1	17	5 males + 5 Females
2	33	5 males + 5 Females
3	65	5 Males + 5 Females
4	130	5 males + 5 Females
5	250	5 males + 4 Females

Dose Selection: Based on a previous dose selection study.

RESULTS:

OBSERVED EFFECTS:

Group	Dose (ug/kg)	# of Animals and finding
0	0	None
1	17	None
2	33	3 m: Transiently, reduced motility, dyspnea, hyporeactivity, and abdominal position. Decreased defecation for both males and females.
3	65	2 m, 2 f: Transiently reduced motility, dyspnea, hyporeactivity, and abdominal position (males only). Decreased defecation for both males and females.
4	130	3 m, 3 f: Transiently reduced motility, dyspnea, hyporeactivity, and abdominal position (males only). Decreased defecation for both males and females.
5	250	4 m, 2 f: Transiently reduced motility, hyporeactivity, and dyspnea. Decreased defecation for both males and females.

MORTALITY:

Group	Dose (ug/kg)	# of Deaths
0	0	None

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1	17	None
2	33	2 males on day 3, 3 males on day 4.
3	65	2 females on day 3, 2 males on day 4,
4	130	3 males and 3 females on day 3, 2 females on day 4.
5	250	All 5 males and 5 females died on days 2-4.

BODY WEIGHT:

Group:	Dose (ug/kg):	Finding:
0	0	None
1	17	Transient 10% weight loss, normal weight gain thereafter.
2	33	Transient 10% weight loss, normal weight gain thereafter.
3	65	Transient 10% weight loss, normal weight gain thereafter.
4	130	Transient 10% weight loss, normal weight gain for males thereafter, females died.
5	250	~ 10% weight loss, all animals died by day 4.

FOOD CONSUMPTION: Not determined.
EYE EXAMINATION: Not determined.
HEMATOLOGY and COAGULATION: Not determined.
BLOOD CHEMISTRY: Not determined.
URINALYSIS: Not determined.
ORGAN WEIGHTS: Not determined.

NECROPSY FINDINGS:

Group:	Dose (ug/kg):	# of Animals and finding:
0	0	None.
1	17	None.
2	33	Lung congestion, tan foci on the heart in the deceased animals, no observed effects in the surviving necropsied animals.
3	65	Lung congestion, tan foci on the heart and foci on the surface of kidneys in the deceased animals at all doses, no observed effects in the surviving necropsied animals.
4	130	Lung congestion, tan foci on the heart and foci on the surface of kidneys in the deceased animals at all doses, no observed effects in the surviving necropsied animals.
5	250	Lung congestion, tan foci on the heart and foci on the surface of kidneys in the deceased animals at all doses, no observed effects in the surviving necropsied animals.

GROSS and HISTOPATHOLOGY:
Not determined except as noted above for necropsy findings.

SUMMARY and CONCLUSIONS:

Common dose dependent findings were weight loss, reduced activity, and tan foci on the hearts. Red foci on the kidneys and congestion of the lungs were noted in the deceased animals. These toxicities reflect the pharmacological effect of the drug to cause hypercalcemia.

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Route:	Minimal lethal dose (ug/kg)	HED* (ug/kg) based on mg/m^2 comparison	LD-50 (ug/kg)	HED* (ug/kg)	Human dose multiple**
I. P. males	33	6	25	4	25 x
I. P. females	65	10	70	12	75 x

*** HED = human equivalent dose on mg/m2 basis**
**** assume human dose of 10 ug**

Males appear to be slightly more sensitive to the drug, dying sooner and at slightly lower doses. The minimum lethal dose and the LD-50 are very close together indicating a very steep toxicity curve. However, this LD-50 (I. P.) is ~25-75-times the proposed human oral dose (10 ug) when doses are compared on a mg/m^2 basis. The validity of this comparison is discussed in the ADME section of this review.

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Four-Week Comparative Toxicity Study of [redacted]870 and 1α-OH-D_3 via oral Gavage in Rats ([redacted]14-90)

PURPOSE:

To assess and compare the toxicity of Hectorol (1α-OH-D_2) and 1α-OH-D_3 when administered orally to rats for one month.

EXPERIMENTAL DESIGN:

Testing Facility: [redacted]
Study #: [redacted]14-90
Study Initiated: Not reported
Study Completed: 4/22/92
Dose & Formulation: 0, 0.1, 0.5, 2.5, 12.5 ug/kg/day oral. Gavage in 1 ml/kg/d of coconut oil.
Batch of drug: lot Ecl α OH927904, crystalline form of TSA-870 (1α-OH-D_2) Lot Cc1 α OH211911 for 1α-OH-D_3.
Food: Commercial rodent chow, CE-2, [redacted]
GLP statement: Included and signed.
Animals: Male Crj:CD rats were purchased from [redacted] 6 weeks old, 192-236 g.

Group:	Dose (ug/kg/day):	# of Animals:
[redacted]870:		
1	0	10 males
2	0.1	10 males
3	0.5	10 males
4	2.5	10 males
5 1α-OH-D_3	12.5	10 males
6	0.1	10 males
7	0.5	10 males
8	2.5	10 males
9	12.5	10 males

Rats were allowed free access to food and water.

Plasma levels: Levels of parent compounds and active metabolites were measured in separate groups:

Group:	Dose (ug/kg/day):	# of Animals:
[redacted]870:		
1	0	24 males
3	0.5	21 males
4 1α-OH-D_3	2.5	21 males
7	0.5	21 males
8	2.5	21 males

Dose Selection: Based on a previous dose selection study, doses were selected to demonstrate differences in the concentration / toxicity relationship.

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RESULTS:

OBSERVED EFFECTS:

Group:	Dose (ug/kg/day):	# of Animals and finding:
[redacted]870:		
1	0	None
2	0.1	None
3	0.5	None
4	2.5	None
5 1α-OH-D_3	12.5	Wasting, 3/10, after week 3.
6	0.1	None
7	0.5	None
8	2.5	Wasting 3/10, after week 3.
9	12.5	Wasting 7/10, after week 3.

MORTALITY:

No animals died in any group or portion of the study.

BODY WEIGHT:

Group:	Dose (ug/kg/day):	Finding:
[redacted]870:		
1	0	None
2	0.1	None
3	0.5	None
4	2.5	None
5 1α-OH-D_3	12.5	Body weight gain was significantly decreased compared to control from day 7 onward (23% difference in weight from controls).
6	0.1	None
7	0.5	None
8	2.5	None
9	12.5	Body weight gain was significantly decreased compared to control from day 7 onward (40% difference in weight from controls).

FOOD and WATER CONSUMPTION:

Group:	Dose (ug/kg/day):	Finding:
[redacted]870:		
1	0	None
2	0.1	None
3	0.5	None
4	2.5	None
5	12.5	Food consumption was decreased compared to control (23%) while water consumption was increased 51% (NS) and urinary output was increased 120% (NS).

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Group:	Dose (ug/kg/day):	Finding:
1α-OH-D_3		
6	0.1	None
7	0.5	None
8	2.5	None
9	12.5	Food consumption was decreased compared to control (55 %) while water consumption was increased 62% (NS) and urinary output was increased 160% (NS).

EYE EXAMINATION: Not determined.

HEMATOLOGY and COAGULATION:

Group:	Dose (ug/kg/day):	Finding:
[redacted]870:		
1	0	None
2	0.1	None
3	0.5	None
4	2.5	None
5 1α-OH-D_3	12.5	Platelets decreased (21%) vs. controls.
6	0.1	None
7	0.5	None
8	2.5	None
9	12.5	Platelets (48%) and leucocytes (primarily lymphocytes) decreased (43%), erythrocytes increased (6%) vs. controls.

BLOOD CHEMISTRY:

Group:	Dose (ug/kg/day):	Finding:
[redacted]		
1	0	None
2	0.1	None
3	0.5	None
4	2.5	Increased calcium (15 %)
5 1α-OH-D_3	12.5	Increased calcium (32 %) and cholesterol (30 %) Decreased inorganic phosphorous (9 %) and potassium (16 %).
6	0.1	None
7	0.5	Increased calcium (9 %)
8	2.5	Increased calcium (28 %)
9	12.5	Increased calcium (32 %), cholesterol (80 %), ALP (53 %), and LAP (29 %). Decreased inorganic phosphorous (15 %) and potassium (12 %).

Only the effects on calcium, potassium and cholesterol are large enough to be statistically and physiologically meaningful.

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URINALYSIS:

Group: [redacted]870:	Dose (ug/kg/day):	Finding:	Creatinine:	Calcium:	Phosphorous:
1	0	None	67	0.07	0.9
2	0.1	None	72	0.07	1.0
3	0.5	None	62	0.5	1.66
4	2.5	Decreased pH (to 7).	46	**1.5****	**2.91****
5 1α-OH-D_3	12.5	**Decreased pH (to 6)**	**40***	**2.4****	**3.93****
6	0.1	None	62	0.29	1.73
7	0.5	Decreased pH (to 7)	59	**1.45****	**2.67****
8	2.5	**Decreased pH (to 6)**	**45***	**2.21****	**3.78****
9	12.5	**Decreased pH (to 5)**	**30****	**2.55****	**4.31****

ORGAN WEIGHTS:

Ventral prostate weight was significantly decreased (40-50%) compared to control in the HD of both drugs. Other statistically significant decreases were consistent with decreases in body weight described above, only the ventral prostate weight was decreased relative to body weight.

NECROPSY FINDINGS:

Group: [redacted]870:	Dose (ug/kg/day):	Finding:
1	0	No drug related findings.
2	0.1	No drug related findings.
3	0.5	No drug related findings.
4	2.5	No drug related findings.
5 1α-OH-D_3	12.5	4/10 pale kidneys, 5 white foci on kidneys, 1/10 atrophy of prostate and seminal vesicles.
6	0.1	No drug related findings.
7	0.5	No drug related findings.
8	2.5	No drug related findings.
9	12.5	9/10 pale kidneys, 8 white foci on kidneys, atrophy of: prostate (8/10), seminal vesicles (5/10), thymus (5/10), liver (2/10), spleen (1/10), testes (1/10).

HISTOPATHOLOGY:

Group: [redacted]870:	Dose (ug/kg/day):	Finding:
1	0	None
2	0.1	None
3	0.5	(2/10) Increased bone formation in femur and sternum *,
4	2.5	(9/10) Increased bone formation in femur and sternum *, (5/10) mild calcification of renal tubules.

5 1α-OH-D_3	12.5	(10/10) Increased bone formation in femur and sternum *, (9/10) mild-moderate calcification & (4/10) dilatation & degeneration of renal tubules, calcification of (5/10) fundic mucosa, (4/10) arteries of the tongue, (2/10) myocardium, (2/10) arteries of stomach, (2/10) hypertrophy of zona fasiculata.
6	0.1	(2/10) Increased bone formation in femur and sternum *,
7	0.5	(6/10) Increased bone formation in femur and sternum *, (6/10) mild-moderate calcification of renal tubules.
8	2.5	(10/10) Increased bone formation in femur and sternum *, (7/10) calcification and (1/10) dilatation of renal tubules, (2/10) mild-moderate calcification of the fundic mucosa.
9	12.5	(10/10) Increased bone formation in femur and sternum *, (9/10) moderate calcification & (4/10) dilatation & degeneration of renal tubules, calcification of (10/10) fundic mucosa, (8/10) arteries of the tongue, (5/10) myocardium, (2/10) arteries and (2/10) muscles of stomach, (1/10) slight hyperkeratosis of skin (3/10) hypertrophy of zona fasiculata (1/10) single cell necrosis in the zona reticularis.

*Bone changes were characterized by: dose dependent increases in cancellous bone in the metaphysis and epiphysis and the marrow space associated with decreased marrow space, enlarged osteocytes and hypertrophy of osteoblasts.

Additional calcification of renal pelvic epithelium, cornea, salivary gland, tracheal mucosa, and dilation of the fundic glands was observed in small numbers of treated animals.

PHARMACOKINETICS:

Both [redacted]870 (1α-OH-D_2) and 1α-OH-D_3 are hydroxylated at the 25-position in the liver to produce the active forms of Vitamin D, (OH2-D2:) 1α,25-$(OH)_2$-D_2 and (OH2-D3:) 1α,25-$(OH)_2$-D_3, respectively. In addition, all mammals produce D2 and D3 endogenously. In order to compare exposure to active vitamin D in the [redacted]870 (1α-OH-D_2) and 1α-OH-D_3 groups the plasma levels of OH2-D2 and OH2-D3 were assayed on Day 1and Day 15.

DAY 1:

Dose & Compound	AUC (0-24), pg*h/ml		
	1α,25-$(OH)_2$-D_2	1α,25-$(OH)_2$-D_3	Total
Control	863	1458	2321
0.5 ug [redacted]870	1772	1007	2779
2.5 ug [redacted]870	4291	1095	5385
0.5 ug 1α-OH-D_3	774	3841	4615
2.5 ug 1α-OH-D_3	421	6215	6636

DAY 15:

Dose & Compound	AUC (0-24), pg*h/ml		
	1α,25-$(OH)_2$-D_2	1α,25-$(OH)_2$-D_3	Total
Control	787	1317	2103
0.5 ug [redacted]870	2733	0	2733
2.5 ug [redacted]870	5236	0	5236
0.5 ug 1α-OH-D_3	0	3626	3626
2.5 ug 1α-OH-D_3	0	6857	6857

1. Plasma levels of both metabolites rose dose-dependently after administration of doses of 0.5 and 2.5 ug/kg of [redacted]870 (1α-OH-D_2) and 1α-OH-D_3.
2. Exposure to OH2-D3 was higher than exposure to OH2-D2 for the same dose of both drugs.

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3. After 15 days of dosing there is no more production of 1α,25-$(OH)_2$-D_2 in the group given the D3 analog, and there is no more production of 1α,25-$(OH)_2$-D_3 in the group given the D2 analog.
4. The AUCs for the total active metabolites for each dose of each drug do not change much from Day 1 to Day 15. The reduction in the levels of the endogenous active metabolites is probably related to an increased production of metabolite from exogenous precursor.

SUMMARY and CONCLUSIONS:

In rats, similar dose dependent findings were reported when animals were dosed with either 1a-OH-D2 or 1a-OH-D3 analog. The findings reflected the physiologic actions of vitamin D: Diminished weight gain, hypercalcemia with calciuria and phosphaturia, pale kidneys with white foci, calcification of myocardium, selected blood vessels, gastric mucosa, muscle and kidney with accompanying tubular degeneration. Dose dependent, increased proliferation of cancellous bone was a common finding and (when severe) may affect bone marrow function, resulting in hematological changes. All of these effects reflect the pharmacological actions of Vitamin D and are consistent with results from other toxicity tests.

Route:	NOAEL (ug/kg/d)	HED* (ug/kg/d)	Human dose multiple**
[redacted]-870	0.1	0.017	0.24 x
1α-OH-D_3	< 0.1	< 0.017	< 0.24 x

* HED = human equivalent dose on a mg/m^2 basis

** Assume human dose of 3x10 ug/week, ie, 4.3 µg/day, ie, 0.07 µg/kg/day

The NOAEL for [redacted]870 in this 28-day rat study was 0.1 ug/kg/day. This dose is below the proposed human equivalent exposure (0.24x, on a mg/m^2 basis).

The fact that the NOAEL for 1α-OH-D_3 was smaller than for [redacted]870 is in accordance with the finding that the toxicities in a 1α-OH-D_3 dose group were equivalent with the toxicities seen in a [redacted]870 group at 2-5 fold higher doses. This is surprising due to the fact that vitamin D_2 analogs generally have similar activity as their corresponding vitamin D_3 analogs. The finding can partially be explained by the pharmacokinetic analysis which showed that exposure to active metabolite in the D_3 treated group was somewhat higher than in the [redacted]870 (D2) treated group.

The sponsor concludes from this study that in male rats [redacted]-870 is 5 times less toxic than 1α-OH-D_3. This reviewer would agree that in male rats [redacted]870 is less toxic than 1α-OH-D_3, but it is likely that it is also less potent. This study does not prove any more general claim about the relative toxicity, potency or therapeutic index of [redacted]-870

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13-Week Oral Toxicity Study in Rats ([redacted]615-002)

Summary Review
(Complete Review attached in Appendix)

SUMMARY TABLE

(Table lists all statistically significant findings. See attached review for details.)

EFFECT/DOSE	0	0.06 ug/kg/d	0.39 ug/kg/d	2.5 ug/kg/d
Number/sex:	15	15	15	15
CLINICAL SIGNS:		No treatment related effects (TRE).		
MORTALITY (M/F):		1(accident)/0	0/0	1/0
BODY WEIGHT:			Decreased (females)	Decreased (M & F)
FOOD CONSUMPTION:		No TRE.	Some individuals decreased consumption.	Some individuals decreased consumption
HEMATOLOGY:		No treatment related effects.		
BLOOD CHEMISTRY:		No TRE.	⇑Ca (slightly in males)	⇑Ca (in males) ⇑P (in males and females)
URINALYSIS:		No TRE.	⇑ Ca, P, P/creatinine and Ca/creatinine.	
ORGAN WEIGHTS:		No TRE.	No TRE.	Increased adrenal weight
GROSS PATHOLOGY:		1 male from each group had calculi of the kidney or bladder.		
HISTO-PATHOLOGY:		No TRE.	11 males and 12 females from each group had renal pelvic calculi (severe in the HD group). Renal microconcretions were present in 27% MD 86% HD. 1 dead HD male had myocardial, vascular, renal calcification, pyelonephritis and cystitis.	

TRE = treatment-related effect

SUMMARY and CONCLUSIONS:

Drug:	NOAEL (ug/kg/day)	HED* (ug/kg/day)	Human dose multiple**
TSA-870:	0.06	0.01	0.143 x

* HED on a mg/m^2 basis.

** Assume human dose of 3x10 ug/week = 0.07 µg/kg/day

Dose dependent toxic effects of Hectorol reflected the physiologic actions of vitamin D: Diminished weight gain, renal calcification, hypercalcemia with calciuria and phosphaturia and calcification of myocardium. All of these effects reflect the pharmacological actions of Vitamin D and are consistent with results from other toxicity testing. The dose of [redacted]-870 that did not produce any observed adverse effect (NOAEL) was 0.06 ug/kg/d. This dose is below the proposed human equivalent dose (0.14x, on a mg/m^2 basis).

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One year Oral Toxicity Study in Rats [redacted] 295-136)

Summary Review
(Complete review attached in Appendix)

SUMMARY TABLE

(Table lists all statistically significant findings. See attached review for details.)

EFFECT/DOSE:	0	0.02 ug/kg/d	0.06 ug/kg/d	0.55 ug/kg/d	5 ug/kg/d
Number/sex:	25	25	25	25	25
MORTALITY (M/F):	0/0	1/1	0/1	2/1	24/18
CLINICAL SIGNS:		No TRE	labored breathing in 6 females	Hunched posture, labored breathing, reduced activity, decreased defecation and stained fur.	
BODY WEIGHT:		No TRE	Slightly increased wt. Gain in males	Decreased wt gain, 15% f, 20% m	Decreased wt gain, 15% f, 20% m
FOOD CONSUMPTION:		No TRE	No TRE.	Some individuals increased consump.	More variable food consumption.
HEMATOLOGY:		No TRE	No TRE.	Decreased RBC, Hct. and hemoglobin. Increased reticulocytes.	Decreased RBC, hematocrit and hemoglobin. Increased reticulocytes.
BLOOD CHEMISTRY:		No TRE	No TRE.	⇑ Ca & ⇑ P	⇑ Ca & ⇑ P in M & F. ⇑ AP and AST in females.
URINALYSIS:		No TRE	⇑ Ca (M), ⇑ Ca/creat. (M&F).	⇑ Ca, ⇑ P, ⇓ pH, (M&F), ⇑ P/creatinine (M).	⇑ Ca, ⇑ P, ⇑ P/creatinine ⇓ pH, in both sexes.
ORGAN WEIGHTS:			Changes in absolute organ weights consistent with reductions in body weight.		Trend toward drug related decrease in liver weight but too many deaths to be clear.

GROSS and HISTOPATHOLOGY:

EFFECT/DOSE (ug/kg/d)	Incidence of treatment related pathological findings (M/F):				
	0	0.02	0.06	0.55	5.0
Thickening of bones: costrochondal junction sternum, & vertebrae		No TRE	No TRE	CJ: 19/9 mild St: 3/2 mild Vt: 11/2 mild	CJ 24/20 mild-moderate St: 3/19 mild – moderate Vt. 27/22 mild moderate
Thickening of blood vessels: Aorta, mesenteric and stomach. (all mild-mod)		No TRE	No TRE	Aorta, 1 mild (F)	Aorta, 17/14, Stomach 2/3 Mesenteric 6/6
Tan foci on heart		No TRE	No TRE	0	5 males, 2 females
Discolored, firm or swollen prostate		No TRE	1 severe	1 moderate	4 mild-severe
White foci on stomach		No TRE	No TRE.	1 M	15/13 F, (trace-mild)
Hyperostosis: Thickening of cortical and trabecular bone with marrow reduction		No TRE	No TRE	12/21 mild 11/3 moderate	35/27 moderate
Extramed. hematopoesis in spleen, liver & adrenal		No TRE	No TRE.	13/11 trace 5/5 mild	1/5 trace 3/10 mild
Mineralization of aorta		No TRE	No TRE.	2/0 moderate	20/9 mild, 15/10 moderate
Mineralization of kidney (pelvic, tubular, vascular)		No TRE	No TRE	11/6 mild 2/2 moderate	10/15 mild 25/8 moderate

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Mineralization of heart		No TRE	No TRE.	5/2 mild 9/ moderate	22/18 moderate 13/6 severe
Cardiomyopathy				6/2 trace 3/2 mild	12/8 mild, 8/4 moderate 1/1 severe

TRE = treatment-related effects

Note: * Bone spleen liver heart and kidney were the only organs examined microscopically from mid-dose groups. Histopathology results for the 0.55 ug/kg/d group were submitted on December 30, 1998 (see Addendum below).

SUMMARY and CONCLUSIONS:

Drug:	NOAEL (ug/kg/day)	HED* (ug/kg/day)	Human dose multiple**	LOAEL (ug/kg/day)	HED* (ug/kg/day)	Human dose multiple**
[redacted]-870:	0.02	0.003	0.048 x	0.06	0.009	0.14 x

* HED on a mg/m^2 basis.

** Assume human dose of 3x10 ug/week = 0.07 µg/kg/day

Dose dependent toxic effects of Hectorol reflected the physiologic actions of vitamin D: Diminished weight gain, renal calcification, hypercalcemia with calciuria and phosphaturia and calcification of blood vessels in numerous organs with accompanying tissue damage. All of these effects reflect the pharmacological actions of Vitamin D and are consistent with results from other toxicity testing. One effect, which was seen clearly for the first time in this study, was the hyperostosis in bone. This effect was dose dependent and was seen to some extent in all bones. This effect was not observed in shorter-term studies because it takes a long time to develop. In moderate to severe cases the hyperostosis lead to diminished medullary space. This may be the cause of the extramedullary hematopoiesis and the changes in hematology.

The dose of [redacted]-870 that did not produce any observed adverse effect (NOAEL) was 0.02 ug/kg/d. This dose is below the proposed human equivalent dose (0.048x, on a mg/m^2 basis). The LOAEL was 0.14x the human equivalent dose. However, this does not necessarily cause concern about the proposed human dose because the toxicities all appear to result from the pharmacological actions of the drug. Moreover, the human dose multiple of this NOAEL calculated by mg/m^2 comparison is an underestimate of the human exposure multiple (see ADME section, p.62). Nevertheless, the toxic effects suggest significant risks of relatively short-term exposure to Vitamin D in excess of the levels required to normalize calcium and PTH levels in patients.

ADDENDUM
ONE-YEAR ORAL TOXICITY STUDY IN RATS ([redacted]295-136)

Submission: December 30, 1998 (NDA Supplement Vol. 16.1)
Content of submission: Draft histopathology report on tissues from rats in next-to-highest dose group (0.55 ukd).

BACKGROUND

In the original study report of the one-year rat oral toxicity study, only microscopic data on tissues from highest dose group (Group 5, 5 ukd), and - if treatment-related lesions occurred also on tissues from next lower dose group (Group 4, 3, 2) - were presented. However, since there was a high mortality rate in the high dose Group 5, Dr. Coleman requested data on all major tissues from the next lower dose Group 4 (0.55 ukd), regardless of findings in Group 5. The current NDA amendment contains an unaudited draft report with the requested data. Final report will be submitted by January 31, 1999. The original review of

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540 (Review Date 4/3/96, see Appendix).

METHODS

Charles River Crl CD rats (35/sex) were doses orally, by gavage with 1a-OH-D2 dissolved in fractionated coconut oil with 0, 0.02, 0.06, 0.55, 5 ukd. After 6 months, 10/sex/group were sacrificed. Blood samples were collected at 4, 8, 24h post dose from 10/sex after 6 months, and from survivors after 12 months. In the original study all tissues were examined from control and HD rats. In addition, bone and bone marrow (femur and sternum, rib, thoracic vertebrae), spleen, liver, kidney, heart, and gross lesions were examined in all treated groups (Group 1,2,3,4,5). Current report contains data on histopathology of all tissues in Group 4 (0.55 ukd), and on tissues with treatment-related findings in Group 4 from all other dose groups (Groups 2,3).

RESULTS

Survival

Group	Dose	M	F
1	0	25	25
2	0.02	24	24
3	0.06	25	24
4	0.55	23	24
5	5	01	07

Body weight

BW gain decreased in Group 3, 4, 5, and in females of Group 4, 5.

Gross Pathology

Thickening of bones (sternum and vertebrae) in Groups 4, 5.
Thickening of soft tissues (aorta, mesenteric blood vessels, stomach serosal blood vessels) Groups 4,5.
Findings more severe in m than in f.

Histopathology

TREATMENT-RELATED FINDINGS

MALES
DOS= died on study, SAC = sacrified

	Group		2	2	3	3	4	4
Dose (ukd)			0.02	0.02	0.06	0.06	0.55	0.55
			DOS	SAC	DOS	SAC	DOS	SAC
			(2)	(24)	(0)	(25)	(2)	(23)
Aorta	Mineralization		0/2	nd	0/0	nd	1/2	4/23
Bone (Femur, Rib, Sternum, Vertebrae)	Hyperostosis	mild to moderate	0/2	0/24	0/0	0/24	2/2	23/23
Eye	Mineralization	mild to moderate	0/2	0/3	0/0	0/3	1/2	9/23
Heart	Vascular mineralization	trace to moderate	0	0	0	1	2	14
	Cardiomyopathy		1	3	0	9	1	8
Kidney	Renal cell adenoma		0	0	0	0	0	1
	Chronic nephritis		1	18	0	23	0	20
	Vascular/pelvic/tubular mineralization		1	1	0	1	2	22
Larynx	Inflammation	mild to severe	1/2	nd	0/0	nd	1/2	9/23
	Mineralization	mild to moderate	0/2	nd	0/0	nd	0/2	12/23
Liver	Extramedullary hematopoiesis		0	0	0	0	1	12
Lung	Mineralization		0/2	nd	nd	nd	0/2	2/23
	Vascular mineralization	mild	1/2	nd	nd	nd	2/2	14/23

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Lymph node, mandibular	Hemorrhage	trace to moderate	0/2	nd	nd	nd	0/2	10/22
Nerve, sciatic	Mineralization		0/2	nd	nd	nd	0/1	7/23
Prostate	Inflammation		1/2	nd	nd	nd	2/2	4/23
	Mineralization	moderate	0/2	nd	nd	nd	0/2	1/23
Salivary gland, mandibular	Vascular mineralization		0/2	nd	nd	nd	1/2	7/23
Spleen	Increased extramedullary hematopoiesis	mild to moderate	0	4	0	4	1	23
Stomach, glandular	(Vascular) Mineralization	mild	0/2	nd	nd	nd	2/2	5/23
Trachea	Mineralization		0/2	nd	nd	nd	1/2	8/23
Endocrine system:								
Adrenal medulla	Hyperplasia	Total	0	1	0	16	0	16
		trace	0	1	0	13	0	0
		mild	0	0	0	3	0	15
		moderate	0	0	0	0	0	1
Pituitary	Adenoma		0/2	1/1	0/0	nd	0/2	1/22
	Cyst		0/2	0/1	0/0	nd	0/2	2/22
Thyroid	C-cell hyperplasia	mild	0/2	nd	nd	nd	0/2	1/23

nd = no data (no animals examined)

FEMALES

	Group		2	2	3	3	4	4
Dose (ukd)			0.02	0.02	0.06	0.06	0.55	0.55
			DOS	SAC	DOS	SAC	DOS	SAC
			(2)	(24)	(1)	(24)	(2)	(24)
Bone (Femur, Rib, Sternum, Vertebrae)	Hyperostosis	trace to moderate	0	0	0	0	2	24
Eye	Mineralization	trace to mild	0/2	0/5	0/1	0/2	1/2	5/24
Heart	Vascular mineralization	trace to mild	0	0	0	0	1	3
	Cardiomyopathy		0	1	0	4	2	2
Kidney	Chronic nephritis		1	9	0	11	1	18
	Vascular/pelvic/tubular mineralization		0	17	1	11	2	24
Larynx	Inflammation	trace to moderate	0/2	nd	0/1	nd	1/2	8/24
	Mineralization	mild	0/2	nd	0/1	nd	1/2	5/24
Lung	Vascular mineralization	mild	1/2	nd	1/1	nd	2/2	15/24
Lymph node, mandibular	Hemorrhage	mild to moderate	1/2	nd	0/1	nd	0/2	7/24
Lymph node, mediastinal	Hemorrhage	mild	0/2	nd	0/1	nd	0/2	4/24
Spleen	Increased extramed hematopoiesis	mild to moderate	0	9	0	7	1	18
Uterus	Cystic dilatation		0/2	nd	0/1	nd	0/2	3/24
	Squamous metaplasia	mild	0/2	nd	0/1	nd	0/2	3/24
	Polyp		0/2	nd	0/1	nd	0/2	1/24
Cervix	Cystic dilatation	mild	0/2	nd	0/1	nd	0/2	1/24
Mammary region	Adenoma		0/2	0/1	0/1	nd	0/2	1/24
	Cystic dilation	mild to moderate	1/2	1/1	1/1	nd	0/2	5/24
	Lobular hyperplasia	mild	0/2	0/1	0/1	nd	0/2	1/24
Endocrine system:								
Adrenal medulla	Hyperplasia	Total	0	1	0	12	0	15
		trace	0	1	0	11	0	1
		mild	0	0	0	1	0	14
Pituitary	Adenoma		0/2	nd	0/1	1/1	0/2	2/24
	Cyst	mild	0/2	nd	0/1	0/1	0/2	1/24
	Hyperplasia	mild	0/2	nd	0/1	0/1	0/2	6/24
Thyroid	C-cell hyperplasia	mild	0/2	0/1	0/1	nd	0/2	2/24

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CONCLUSIONS

1. Main histopathology findings in Group 4 (0.55 ukd) were bone endosteal hyperostosis (thickening of cortical and trabecular bone), partial obliteration of bone marrow, extramedullary hematopoiesis in liver and spleen, and soft tissue mineralization. All of these findings had also been seen in Group 5.
2. The NOAEL as determined from the main report of the 1-year rat toxicity study was 0.02 ukd, and the LOAEL was 0.06 ukd. The current additional study results suggest the same adverse effect evels. The LOAEL of 0.06 ukd corresponds to a human exposure multiple of appr. 1.2x (see ADME section, p.62).
3. A new additional finding in Group 4 was hyperplasia of the adrenal medulla. The latter was also seen in Group 3 (0.06 ukd), but not in Group 2 (0.02 ukd). In long term toxicity studies in rats, adrenal medullary hyperplasia often occurs in conjunction with other endocrine tissue hyperplasia or neoplasms. It has been claimed to result from high dietary Ca contents. In this study, the vitamin D induced chronic hypercalcemia may be the cause of the adrenal hyperplasia.

Study	NOAEL (ug/kg/day)	HED* (ug/kg/day)	Human dose multiple**	LOAEL (ug/kg/day)	HED* (ug/kg/day)	Human dose multiple**
1-year rat	0.02	0.003	0.048 x	0.06	0.009	0.14 x

* HED on a mg/m^2 basis.

** Assume human dose of 3x10 ug/week = 0.07 µg/kg/day

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Two-Week Oral Toxicity Study in Cynomolgus Monkeys ([redacted]-14-28)

PURPOSE:

To assess the toxicity of Hectorol in monkeys when administered orally for 2 weeks.

EXPERIMENTAL DESIGN:

Testing Facility: [redacted]
Study #: [redacted]14-28
Study Initiated: 10/23/90
Study Completed: 1/25/91
Dose & Formulation: 0, 6, 20, & 60 ug/kg oral single dose, in 1 ml/kg of coconut oil.
Batch of drug: lot K004.
Food: Purina certified primate chow 5048.
Monkeys were allowed free access to food and tap water.
GLP statement: None
Animals: 8 Cynomolgous monkeys were obtained from [redacted] Primate.

Group:	Dose (ug/kg):	# of Animals:
0	0	1 male + 1 Female
1	6	1 male + 1 Female
2	20	1 male + 1 Female
3	60	1 male + 1 Female

Dose Selection: Based on the results of the 13-week monkey study (below).

RESULTS:

SUMMARY TABLE

(Table lists all statistically significant drug related findings. See attached review for details.)

EFFECT/DOSE:	0	6 ug/kg/d	20 ug/kg/d	60 ug/kg/d
Number/sex:	1	1	1	1
MORTALITY (M/F):	0/0	0/0	0/0	0/0
CLINICAL SIGNS:		No TRE.		
BODY WEIGHT:		No TRE.		
FOOD CONSUMPTION:		No TRE.		
HEMATOLOGY:		No TRE.		
BLOOD CHEMISTRY:		No TRE.	↑Ca ↑ BUN (in M only)	↑Ca (in F only) ↑ BUN (in F only)
URINALYSIS:		↑P (in F only)	↑P (M & F)	
ORGAN WEIGHTS:		No TRE.		
GROSS PATHOLOGY:		No TRE.		
HISTO-PATHOLOGY:		No TRE.	Slight degeneration of renal tubules (F)	Slight degeneration of renal tubules (M&F)

TRE = treatment-related effect

SUMMARY and CONCLUSIONS:

An oral dose of 6 ug/kg/day of Hectorol can be considered the NOAEL for two weeks in monkeys. Expected vitamin D mediated toxicities (hypercalcemia, phosphaturia, kidney damage) were seen at higher doses. No significant sex related differences in sensitivity.

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Drug:	NOAEL (ug/kg/day)	HED* (ug/kg/day)	Human dose multiple**	LOAEL (ug/kg/day)	HED* (ug/kg/day)	Human dose multiple**
TSA-870:	6	2	29 x	20	6.7	96x

* HED on a mg/m^2 basis.

** Assume human dose of 3x10 ug/week = 0.07 µg/kg/day

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