

NDA 21468

**REVIEW AND EVALUATION OF CANINE TOXICOLOGY
AND PHARMACOKINETICS STUDIES**

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SUBMISSION DATE: April 30, 2002

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SPONSOR: Shire Pharmaceutical Development, Inc.

DRUG: Code Name: SPD 405
Generic Name: Lanthanum (III) Carbonate Hydrate
Trade Name: FOSRENOL™
CAS Number: 544451-24-0

Molecular Formula: $\text{La}_2(\text{CO}_3)_3 \cdot 4 \text{H}_2\text{O}$
Molecular Weight: (anhydrous: 457.8)
Atomic Weight (La): 138.91

FORMULATATION AND ROUTE OF ADMINISTRATION: Chewable tablets for oral administration. Each 250 mg tablet contains 477 mg of lanthanum carbonate hydrate (250 mg lanthanum) and excipients: dextrates — colloidal silicon dioxide — talc — and magnesium stearate — Each 500 mg tablet contains 954 mg of lanthanum carbonate hydrate (500 mg lanthanum) and excipients: dextrates — colloidal silicon dioxide — talc — and magnesium stearate —

PHARMACOLOGICAL CLASS: Phosphate Binding Agent

PROPOSED INDICATION: Ca^{2+}

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PROPOSED DOSAGE REGIME: The proposed initial daily dose is 750 mg lanthanum per day, with an increase of up to 3000 mg lanthanum per day. Lanthanum dose is titrated to that needed to control hyperphosphatemia and given with meals (250 –500 mg lanthanum doses with each meal, dependent on meal size).

IND UNDER WHICH CLINICAL TRIALS WERE CONDUCTED: IND 55054

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¹ Single dose, 4 and 13 week oral toxicology studies were not reviewed since these studies were performed with the same top dose (single dose study) or identical doses (4 and 13 week toxicology studies) as given in the 52 week study. Tissue lanthanum levels and plasma AUCs were not evaluated in these studies. ECGs were not evaluated in any oral toxicology study.

EXECUTIVE SUMMARY

Studies Reviewed

This review was focused on the safety pharmacology, toxicology, pharmacokinetics and toxicokinetics of lanthanum carbonate in dogs. The sponsor did not evaluate the primary pharmacodynamic activity of lanthanum carbonate in dogs.

Safety Pharmacology

A safety pharmacology study in anesthetized dogs, with lanthanum carbonate given as a single intraduodenal dose (200, 600 or 2000 mg/kg), did not reveal cardiovascular safety issues. Lanthanum did not alter ECG parameters, (including QT, QT_{C_{Bazett}}, PR interval), heart rate, systemic blood pressure or left ventricular contractility (LV dP/dt). QRS duration was not reported. Additionally, intravenous administration of up to 1 mg lanthanum chloride/kg/day for 4 weeks did not alter ECG parameters, including QT and QT_{C_{van der Waters}} intervals (toxicology study). The sponsor did not evaluate ECG effects in oral canine toxicology studies with treatment durations of up to 52 weeks.

While in vivo study results are reassuring for lack of cardiac effects, they cannot be considered definitive for the following reasons. First, a single dose safety pharmacology study may be unable to detect lanthanum-related cardiac effects, considering that lanthanum accumulates in canine hearts with repeated daily administration, and tissue lanthanum levels are likely more important than plasma levels for induction of pharmacodynamic effects.² Second, although 4 weeks of daily intravenous lanthanum chloride administration produced relatively high heart lanthanum levels, a positive control was not evaluated in this study, and therefore assay sensitivity is unknown and may be poor.

Oral Toxicology of Lanthanum Carbonate in Dogs

The oral toxicology of lanthanum was evaluated in healthy dogs with dosing durations of up to 52 weeks. Only the 52 week study was reviewed since the lanthanum carbonate doses used were the same (or maximum dose was the same) for all oral toxicology study durations.

Oral administration of 0, 200, 600 and 2000 mg lanthanum carbonate/kg/day for 52 weeks to healthy dogs did not reveal significant toxicity. However, dose related decreases in plasma and urinary phosphate concentration, and urinary phosphate excretion were observed, consistent with lanthanum's primary pharmacodynamic effect of binding phosphate in the gastrointestinal tract. (This activity was not studied in dogs.) Similarly, drug-related increases in urinary calcium concentration and excretion were observed. Oral NOAELs (no observed adverse effect levels) for these findings are shown below.

Finding	NOAEL (mg lanthanum carbonate/kg/day, p.o.)
↓ Plasma phosphate concentration	200 (M), 2000 (F)
↓ Urinary phosphate concentration	<200 (M and F)
↓ Urinary phosphate excretion	600 (M), 2000 (F)
↑ Urinary calcium concentration	600 (M and F)
↑ Urinary calcium excretion	200 (M), <200 (F)

An electron microscopy study evaluating transmural stomach samples from lanthanum treated dogs (52 week oral toxicity study) showed macrophages with electron dense inclusions (or bodies) within the cytoplasm, consistent with macrophages engulfing foreign bodies or particles (lanthanum in this case). No degenerative changes were observed

² See page 5 Lanthanum Levels in Canine Hearts

in those macrophages that contained electron dense inclusions. Findings were similar in stomach samples from rats and mice given lanthanum carbonate chronically for approximately two years.

Pharmacokinetics and Toxicokinetics in Dogs

Lanthanum carbonate was absorbed following oral administration to healthy dogs, although bioavailability was extremely low. Average bioavailability for both sexes is estimated to be 0.00005%

Sex	AUC _{0-24 hr} (ng·hr/ml)		F (%)
	Oral (2000 mg/kg/day)	Intravenous (0.003 mg/kg/day)	
Male	14.61	36.72	0.00006
Female	9.01	33.85	0.00004

AUCs shown are Day 1 values (4-Week Oral Administration Study, SPD0100-TK and Intravenous administration study, SPD0104)

Plasma protein binding of lanthanum was high, and similar in canine and human plasma. Plasma protein binding was approximately 98% in canine and human plasma at a lanthanum concentration of 2.5 ng/ml (98.2% and 97.9% in canine and human plasma, respectively). The median total plasma lanthanum concentration in dogs given 2000 mg lanthanum carbonate/kg/day for 51 weeks was approximately 2 ng/mg.

Following a single oral dose of 1000 mg lanthanum carbonate/kg, lanthanum was eliminated primarily via the fecal route, consistent with low oral bioavailability. However, a small percentage of the administered lanthanum carbonate was recovered in urine (0.2% and 2.0% for the two male dogs evaluated). Most of the lanthanum carbonate administered in this single dose study was recovered in the feces within 24 hours of dosing.

Toxicokinetic analysis in the 52 week oral toxicity study showed dose related plasma and tissue lanthanum exposures. Lanthanum accumulated in most tissues with tissue levels after 26 and 52 weeks of oral dosing that were several orders of magnitude higher than plasma lanthanum levels. Particularly high tissue lanthanum levels were observed in the gastrointestinal system, liver, lungs and bone. Heart lanthanum levels were higher than plasma levels but much lower than those seen in stomach, liver, lungs and bone. Tissue levels for dogs given 2000 mg lanthanum carbonate/kg/day for 52 weeks are shown below.

Tissue	Gender	Median Lanthanum Concentration at 52 wks (ng/g)	Multiple of Median Plasma Lanthanum Concentration at 52 Weeks
Plasma	M	2.24	1
	F	1.77	1
Stomach	M	248,141	110,000
	F	348,949	197,000
Duodenum	M	13055	5828
	F	11364	6420
Colon	M	122281	54,590
	F	24750	13,983
Rectum	M	60612	27,059
	F	35097	19,829
Liver	M	7,251	3200
	F	11,050	6242
Lungs	M	2577	1150
	F	3995	2257
Femur Shaft	M	1843	822
	F	2511	1419
Femur Shaft Marrow	M	1057	471
	F	2856	1613

Tissue	Gender	Median Lanthanum Concentration at 52 wks (ng/g)	Multiple of Median Plasma Lanthanum Concentration at 52 Weeks
Femur Plate	M	3885	1734
	F	3229	1824
Femur Plate Marrow	M	5638	2516
	F	8131	4593
Heart	M	130	58
	F	455	257

Following tissue loading with 4 weeks of oral administration of 2000 mg lanthanum carbonate/kg/day, lanthanum carbonate cleared slowly from several tissues, including several portions of the gastrointestinal tract, liver, lungs, bone and teeth. Shown are combined male and female values. Not all tissues with poor clearance are shown.

Tissue		Median Lanthanum Concentration after 4 Weeks of Treatment (ng/g)	Median Lanthanum Concentration Following 6 Months of Washout (ng/g)	Lanthanum Remaining 6 Months after Treatment Termination (relative to 4 week levels)
Gastrointestinal Tract	Esophagus	94	30	32%
	Stomach (fundus)	8837	4750	54%
	Ileum	1012	165	16%
	Jejunum	60	16	27%
	Duodenum	4294	22	0.5%
	Colon	390	8	2%
	Rectum	12893	33	0.3
Bone and Teeth	Femur shaft	330	167	51%
	Femur growth plate	767	664	87%
	Sternum	40	396	990%
	Teeth	8320	2430	29%
Other organs	Liver	1454	1196	82%
	Lungs	366	126	34%
	Heart	17	<8	<50%

Intravenous Toxicology and Toxicokinetics of Lanthanum Chloride in Dogs

Intravenous administration of 1.0 mg lanthanum chloride/kg/day for 4 weeks to healthy dogs yielded hepatotoxicity associated with higher liver lanthanum levels than those seen with oral dosing at the NOAEL. A 20 fold lower intravenous dose did not yield significant toxicity. NOAELs are provided below for both intravenous (4 week) and oral (52 week) administration studies.

Route	NOAEL for hepatotoxicity	Study Duration	Gender	Liver Lanthanum Concentration (ng/g)
Intravenous*	0.05 mg/kg/day (lanthanum chloride)	4 weeks	Male	18059
			Female	20717
Oral^	2000 mg/kg/day (lanthanum carbonate)	52 weeks	Male	7251
			Female	11050

*Day 25 data for intravenous administration

^ Week 52 data for oral administration (SPD/66/TK)

Intravenous administration of lanthanum chloride yielded high lanthanum levels in bone relative to levels observed with oral administration without evidence of bone toxicity or histopathology. However, exposure at this relatively high level was for only 4 weeks.

Route	NOAEL for bone toxicity	Study Duration	Gender	Femur Lanthanum Concentration (ng/g)	
				Shaft	Growth Plate
Intravenous*	1.0 mg/kg/day (lanthanum chloride)	4 Weeks	Male	26028	45976
			Female	39789	54483
Oral^	2000 mg/kg/day (lanthanum carbonate)	52 Weeks	Male	1843	3885
			Female	2511	3229

*Day 25 data for intravenous administration

^ Week 52 data for femur lanthanum levels (SPD/66/TK)

Lanthanum Levels in Canine Hearts (Oral and Intravenous Lanthanum Administration)

Lanthanum accumulated in heart with repeated daily oral administration, similar to the pattern seen in other tissues. Plasma and heart lanthanum levels were higher at 51 than at 4 weeks of daily oral lanthanum carbonate administration.

Route	Oral Dose	Study Duration	Gender	Lanthanum Concentration	
				Plasma C _{max} (ng/ml)	Heart (Median ng/g)
Oral	2000 mg/kg/day	8 days*	Male	1.29	not determined
			Female	1.57	not determined
		4 Weeks*	Male	11.40	17 (sexes combined)
			Female	10.08	
		25 Weeks^	Male	0.87-17.0	708
			Female	0.63-21.0	484
		51 Weeks^	Male	0.89-20.49	130
			Female	0.87-2.03	455

* Day 8 and Week 4 data from study SPD 0100-TK

^ Weeks 25 and 51 data from study SPD/66/TK (Plasma levels represent a range across the 4 dogs/sex/dose.

Heart lanthanum levels were higher following 4 weeks of intravenous administration of 1 mg lanthanum chloride/kg/day, than with 4 or 51 weeks of oral administration of 2000 mg lanthanum carbonate/kg/day.

Route	Dose	Study Duration	Gender	Heart Lanthanum Concentration (ng/g)
Intravenous*	1.0 mg/kg/day (lanthanum chloride)	4 Weeks*	Male	1518
			Female	2769
Oral^	2000 mg/kg/day (lanthanum carbonate)	4 Weeks#	Male	17 (sexes combined)
			Female	
		51 Weeks^	Male	130
			Female	455

*Day 25 data for intravenous administration

Week 4 data from study SPD 0100-TK

^ Week 51 data for heart lanthanum levels (SPD/66/TK)

Comparison of Lanthanum Exposures in Dogs and Patients

Total plasma lanthanum AUCs in dogs at the oral and intravenous NOAELs were higher than those in dialysis patients given the maximum recommended human dose (MRHD). Although cross-species comparison of tissue lanthanum levels would likely be more appropriate, human tissue lanthanum concentrations are not available.

Species	Health Status	Study Number	Route	Dose (mg lanthanum/kg/day)	Treatment Duration (Days)	Total Plasma AUC _{0-24 hr} (ng.h/ml)	Multiple of Total Human Plasma AUC at the MRHD ^d
Human	Dialysis Patients	LAM-IV-111	Oral	60 ^a (MRHD)	11	31.1	1
Dog	Healthy	SPD0100-TK	Oral	1052 ^b (NOAEL)	42	207	7
						175	6
		SPD0104	I.V.	0.028 ^c (NOAEL)	25	1802	58
						2768	89

a. 3000 mg elemental lanthanum/day/50 kg body weight or 60 mg lanthanum/kg/day (equivalent to 114 mg lanthanum carbonate/kg/day)

b. Elemental lanthanum equivalent to 2000 mg lanthanum carbonate/kg/day (52 week oral toxicity study)

c. Elemental lanthanum equivalent to 0.05 mg lanthanum chloride/kg/day (4 week iv toxicity study)

d. Total (shown) and free (not shown) AUC multiples are similar, since plasma protein binding of lanthanum is similar for humans and dogs.

Conclusions

Oral administration of lanthanum carbonate was not associated with significant toxicity or safety pharmacology effects in dogs. Intravenous administration of lanthanum chloride to dogs at a dose that yielded high plasma and tissue levels induced hepatotoxicity; a 20 times lower intravenous dose did not produce hepatotoxicity. Plasma lanthanum levels at the intravenous NOAEL were 200-300 times higher than those observed in patients given the highest projected clinical dose. However, exposure was for only 4 weeks in the intravenous administration study.

Lanthanum carbonate was absorbed following oral administration. Although bioavailability was extremely low, lanthanum accumulated in canine tissues (particularly gastrointestinal system, liver, lungs and bone) with repeated daily administration, and cleared slowly from these tissues following treatment termination. Toxicity was not observed with oral or intravenous administration in healthy dogs at plasma exposures that are up to 89 times higher than those observed in dialysis patients given the maximum recommended human dose.

Recommendation Regarding Approvability

Canine toxicology, safety pharmacology and toxicokinetic studies support approval of this application.

Recommendation Regarding Labeling³

The proposed **CLINICAL PHARMACOLOGY, Pharmacokinetics** section of the label should address

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The first sentence of paragraph 4 presently reads:

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Change to read:

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³ These recommendations are based on dog data reviewed in this document. Further changes are likely based on additional species evaluated. See main Pharmacology and Toxicology Review by Dr. Xavier Joseph.

SAFETY PHARMACOLOGY STUDIES

Study Titles: Cardiovascular and Respiratory Parameters in the Anesthetized Dog (SPD/64/PH)

Location of Reports: Main Study (SPD/64/PH): Vol 8, pg 001
Analysis of ECGs (SPD/64/a): Vol 8, pg 051

Report Status: Final

Study Initiation Date: 04/16/96

Study Facility: [] 1

GLP Compliance: yes

Animals: Male beagle dogs, 3/dose group, were housed 1-2/galvanized pen and provided with standard dog chow and water *ad libitum*.

Drug: Lanthanum Carbonate
Lot Numbers: 6268/951101, 6268/951201
Route of Administration: intraduodenal
Vehicle: 0.5% w/v carboxymethylcellulose
Dose Levels: 200, 600 and 2000 mg lanthanum carbonate/kg
Treatment Duration: single dose

Observations/Measurements: Systemic arterial blood pressure, heart rate, left ventricular pressure, LVdP/dt, femoral blood flow, respiration rate, tidal volume, minute volume, and lead II ECG (QRS amplitude, PR, ST and QT intervals [uncorrected QT and QT_{C_{Bazen}}]) were monitored in pentobarbital anesthetized dogs. QRS duration was not monitored. Measurements were taken every 30 minutes for 4 hours following dosing. A positive control was not evaluated to demonstrate assay sensitivity.

Drug-Related Findings
There were no drug-related findings.

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TOXICOLOGY STUDIES

Study Title: 52 Week Oral (Capsule) Toxicity Study in the Dog

Location of Report: vol 17, pg 001

Study Number: SPD/66/TK

Report Status: Final

Study Initiation Date: 5, June 1997

Study Facility:

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GLP Compliance: yes

Animals: Male and Female Beagle Dogs

Body Weights: male, 7.3-11.2 kg; female, 6.9-10.6 kg

Number/Sex/Dose: 7 (with 3 sacrificed at week 26 and the remaining 4 sacrificed at week 52)

Age at Initiation of Dosing: 6-8 months

Dogs were housed individually during the day and in pairs at night in galvanized pens and provided with 400 g of pelleted dog diet and water ad libitum. Food was provided as 200 g meals approximately 1.5 hours prior to the 1st and 2nd doses of lanthanum carbonate.

Drug: Lanthanum Carbonate

Lot Numbers: B1066-960803, B 1066-960901 and B1066-960902

Route of Administration: Oral by capsule

Vehicle: empty gelatin capsules

Dose Levels: 0, 200, 600 and 2000 mg lanthanum carbonate/kg/day in two divided daily doses with dose adjusted for most recent body weight. The two daily doses were given approximately 3 hours apart.

Treatment Duration: 52 weeks

Plasma and Tissue Lanthanum Levels: Venous blood samples were taken 1, 2, 4, 6 and 21 hours after the 2nd daily dose (4, 5, 7, 9 and 24 hours after the 1st daily dose) during weeks 25 and 51 for determination of plasma lanthanum levels. Tissue lanthanum levels were determined (see drug-related findings for list of tissues) in dogs sacrificed at 26 and 52 weeks.

Observations/Measurements: Dogs were observed daily for mortality and clinical signs. Body weights and food intake were determined weekly. All dogs were examined ophthalmoscopically prior to start of dosing, and during weeks 25 and 52. Plasma parathyroid hormone and calcitonin levels were determined during weeks 26 and 52 following an overnight fast and prior to the first daily dose of lanthanum. Neurological examinations were performed on all dogs during weeks 26 and 52: anal sphincter tone, pupillary response, gait, proprioception, patella reflex, panniculus reflex, ocular cephalic reflex, palpebral reflex, righting reflex, and withdrawal reflex.

Venous blood and urine samples were taken from all dogs predose, and during weeks 13, 26 and 52 for hematology and clinical chemistry analyses. The following hematology parameters were measured.

Haemoglobin concentration (Hb)
Red blood cell count (RBC)
Packed cell volume (PCV)
Mean cell volume (MCV)

Mean cell haemoglobin (MCH)
Mean cell haemoglobin
concentration (MCHC)

Platelet count (Plate)
Total leucocyte count (WBC) and
leucocyte differential count :
Neutrophil (Neut),
Lymphocytes (Lymph),
Monocytes (Mono),
Eosinophils (Eosin),
Basophils (Baso),
Large unstained cells (Luc)

The following clinical chemistry parameters were measured.

Blood urea nitrogen (BUN)
Creatinine (Creat)
Glucose (Gluc)
Alkaline phosphatase (ALP)
Alanine aminotransferase (ALT)
Aspartate aminotransferase (AST)
Total Protein (T. Prot)
Albumin (Alb)
Globulin (Glob)
Albumin/Globulin ratio (A/G)
Bilirubin (Bili)
Cholesterol (Chol)
Triglycerides (Trigs)
Calcium (Ca)
Inorganic Phosphate (I. Phos)
Sodium (Na)
Potassium (K)
Chloride (Cl)

Coagulation parameters were measured (prothrombin time, fibrinogen, activated partial thromboplastin time).

The following urinalysis parameters were measured.

*Volume

Specific gravity (SG)

Glucose

Bilirubin (Bili)

Ketones

Blood pigments (Blood)

pH

Protein

Urobilinogen (URO)

Nitrites

Leucocytes (L)

Erythrocytes (E)

Crystals (X)

Debris (D)

Casts (C)

Epithelial cells (Epithel cells)

Colour and appearance

*Calcium (Ca)

*Inorganic Phosphorus (I. Phos)

The following organs from all dogs were weighed.

adrenals	brain (incl. cortex)	femur and joint (incl marrow)
heart	duodenum (30cm)	kidneys
liver	lungs	ovaries
pituitary	prostate	salivary glands
spleen	stomach	testes
thymus	thyroids	uterus

Contra lateral organs were weighed together

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The following organs from all dogs were examined microscopically.

adrenals	prostate
aorta	rectum
brain (4 sections)	rib (incl. costochondral junction)
caecum	salivary gland
colon	sciatic nerve
duodenum	site of mammary gland
epididymides	skeletal muscle
eyes (incl. optic nerves)	skin
femur and joint (incl. marrow)	spinal cord (3 sections)
gall bladder	spleen
heart	sternum (incl. marrow)
ileum	stomach
jejunum	submandibular lymph node
kidneys	testes
liver	thymus
lungs (incl. mainstem bronchi)	thyroids (incl. parathyroids)
mesenteric lymph node	tongue
oesophagus	trachea
ovaries	urinary bladder
pancreas	uterus
pituitary	vagina
all gross lesions	

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Results

All dogs survived until scheduled sacrifice. There were no drug-related findings for body weight, food intake, clinical observations or neurotoxicity assessments, ophthalmoscopy, parathyroid hormone levels, hematology or organ weights. Additionally, there were no macroscopic or microscopic findings attributed to lanthanum carbonate administration at 26 weeks (interim sacrifice) or 52 weeks (terminal sacrifice).

Plasma inorganic phosphate levels at week 13 were lower than concurrent control in males given 600 or 2000 mg/kg/day.

Urinary phosphate volume (mg/hr) at week 24 was lower than concurrent control in male dogs given 2000 mg/kg/day. Additionally, urinary phosphate concentration at week 51 was significantly lower than concurrent control in male and female dogs given 200, 600 or 2000 mg/kg/day.

Urinary calcium volume was higher than concurrent control in male dogs given 600 or 2000 mg/kg/day and in female dogs given 200, 600 or 2000 mg/kg/day.

Lanthanum was detected in plasma and tissues from lanthanum carbonate-treated dogs. Plasma levels were dose related, and more uniform at 52 than at 26 weeks of drug treatment. Tissue lanthanum levels were considerably higher than plasma levels in most tissues monitored. Lanthanum levels were highest in gastrointestinal tract (stomach, duodenum and rectum), liver, bone and lungs. Tissue lanthanum levels were similar in dogs sacrificed at 26 and 52 weeks of treatment.

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SUMMARY

Lanthanum Carbonate: 52 Week Oral (Capsule) Toxicity Study in the Dog with a 26 Week Interim Kill

Shire Report No: D00088-LAM-III A	Shire Reference No. : D00088-LAM-III A CRO Study No. : SPD/68/C	Duration of Treatment: 26 or 52 Weeks						
Species/Strain: Beagle Dog	Route: Oral (capsules)	Necropsy Dates Terminal: 9 June 1998						
Weight Range on Day 1: Male = 7.3-11.2g Female = 6.9-10.6g	Test Material: Lanthanum carbonate Batch Nos.: B1066-960803 B1066-960901 B1066-960902	DOSING PERIOD DATES First dose: 5 June 1997 Final dose: 9 June 1998						
Age on Day 1: Approximately 5-7 months old	Vehicle: not applicable	Main Testing Facility: 						
Dosing Frequency: Twice daily. Two equal sub-doses given approximately 3 hours apart.	Dose Volume: not applicable							
Study in Compliance with GLP: Yes								
Data Collected: Toxicokinetics, mortality, clinical observations, body weight, food consumption, ophthalmoscopy, parathyroid hormone levels, haematology, blood chemistry, urinalysis, neurotoxicity, organ weights, macroscopic findings, microscopic findings, tissue analysis for lanthanum levels. This report contains all data collected during the study for animals killed after 52 weeks of treatment, and in-life and tissue lanthanum data only for animals killed after 26 weeks of treatment. Other post mortem observations for animals killed after 26 weeks are reported separately (SPD/68/IK).								
	Male				Female			
Daily Dose (mg/kg/day)	0	200	500	2000	0	200	600	2000
Number of Animals:								
At start of study	7	7	7	7	7	7	7	7
Died or killed moribund	0	0	0	0	0	0	0	0
At Week 26 terminal kill	3	3	3	3	3	3	3	3
At Week 52 terminal kill	4	4	4	4	4	4	4	4
Treatment-related findings are shown; findings considered important are in bold.								
Survival at termination (%):	100	100	100	100	100	100	100	100
Body Weight (g)	No effects of lanthanum carbonate on bodyweight							
Food consumption (g/animal/week)	No effects of lanthanum carbonate on food consumption							
Clinical Observations and Neurotoxicity Assessments	No clinical observations attributable to administration of lanthanum carbonate							
Ophthalmoscopy	No ocular findings associated with lanthanum carbonate administration							
Parathyroid Hormone levels	No treatment-related changes in parathyroid hormone levels							
Haematology Findings	No effects of lanthanum carbonate on haematology measurements							

Dose level (mg/kg/day)	Males				Females			
	0	200	600	2000	0	200	600	2000
Blood Chemistry								
Inorganic phosphate mg/dl - Week 13	6.8	6.4	6.1	5.9	6.3	6.1	6.3	6.4
Urinalysis								
Urine Volume (ml) - Week 24	232	177	448	198	217	202	184	305
Phosphate mg/dl - Week 24	34.1	34.2	21.8	6.8	30.3	36.5	50.5	13.6
Phosphate (volume) mg/hr - Week 24	4.748	2.602	5.717	0.913	3.820	4.088	7.119	2.923
Calcium mg/dl - Week 24	13.6	20.5	10.2	32.7	15.5	18.9	22.3	47.1
Calcium (volume) mg/hr - Week 24	1.698	1.740	2.889	3.317	2.023	2.313	2.068	6.306
Urine volume (ml) - Week 51	204	368	444	309	37	110	260	205
Phosphate mg/dl - Week 51	82.5	67.5	46.5	39.1	129.0	103.5	90.8	64.3
Phosphate (volume) mg/hr - Week 51	9.722	12.980	12.795	6.590	2.359	7.129	10.959	6.125
Calcium mg/dl - Week 51	8.6	7.1	10.0	20.4	14.4	22.2	9.4	27.3
Calcium (volume) mg/hr - Week 51	1.036	1.682	2.763	3.490	0.238	1.286	1.224	3.342
Organ Weights	There were no effects of lanthanum carbonate on organ weights							
Macroscopic Findings	There were no macroscopic findings associated with the administration of lanthanum carbonate.							
Microscopic Findings	There were no microscopic findings associated with the administration of lanthanum carbonate.							
Plasma lanthanum concentrations - Week 26 LLoQ = 19/g								
Range of values at 1,2,4,6 and 24 hours after 2 nd sub-dose								
Sex	Males				Females			
Dose level	Control							
Animal number	41	43	45	47	42	44	46	48
Range (ng/g)	<LLoQ	<LLoQ	<LLoQ	<LLoQ	<LLoQ	<LLoQ	<LLoQ	<LLoQ
Dose level	200 mg/kg/day							
Animal number	55	57	59	61	56	58	60	62
Range (ng/g)	<LLoQ	\	<LLoQ	<LLoQ	<LLoQ	<LLoQ	\	<LLoQ
Dose level	600mg/kg/day							
Animal number	68	71	73	75	70	72	74	76
Range (ng/g)	<LLoQ	\	<LLoQ	\	<LLoQ	<LLoQ	\	<LLoQ
Dose level	2000mg/kg/day							
Animal number	83	85	87	89	84	86	88	90
Range (ng/g)			\					

Plasma lanthanum concentrations - Week 51 LLoQ = $\mu\text{g/g}$									
Range of values at 1,2,4,6 and 24 hours after 2 nd sub-dose									
Dose level	Control								
Animal number	41	43	45	47	42	44	46	48	
Range (ng/g)	<LLoQ	—	<LLoQ	<LLoQ	<LLoQ	<LLoQ	<LLoQ	<LLoQ	<LLoQ
Dose level	200 mg/kg/day								
Animal number	55	57	59	61	56	58	60	62	
Range (ng/g)									
Dose level	600 mg/kg/day								
Animal number	69	71	73	75	70	72	74	76	
Range (ng/g)									
Dose level	2000 mg/kg/day								
Animal number	83	85	87	89	84	86	88	90	
Range (ng/g)									
Wet tissue lanthanum concentration (ng/g) - week 28									
Sex	Male								
Dose level (mg/kg/day)	200			600			2000		
Lanthanum (ng/g)	max	min	median	max	min	median	max	min	median
Brain			42			55			233
Duodenum			249			1810			11123
Femur			175			285			2018
Femur marrow			55			226			1263
Heart			57			146			708
Kidney			123			108			716
Liver			1163			1841			6170
Lungs			225			1044			5270
Spleen			33			47			125
Stomach			8059			10045			8919
Sex	Female								
Dose level (mg/kg/day)	200			600			2000		
Lanthanum (ng/g)	max	min	median	max	min	median	max	min	median
Brain			47			30			44
Duodenum			111			394			5089
Femur			194			692			3264
Femur marrow			115			409			1779
Heart			218			134			484
Kidney			67			132			461
Liver			1604			3690			7430
Lungs			246			321			2634

Sex	Female								
Dose level (mg/kg/day)	200			600			2000		
Lanthanum (ng/g)	max	min	median	max	min	median	max	min	median
Spleen			35			48			134
Stomach			6610			27763			78324

Wet tissue lanthanum concentration (ng/g) – week 52									
Sex	Male								
Dose level (mg/kg/day)	200			600			2000		
Lanthanum (ng/g)	max	min	median	max	min	median	max	min	median
Bone marrow			548			1024			2916
Brain			<13			27			46
Colon			801			27207			122281
Duodenum			189			11995			13055
Femur plate			330			1529			3885
Femur plate marrow			429			3438			5638
Femur shaft			209			728			1843
Femur shaft marrow			132			911			1057
Heart			20			504			130
Kidney			89			297			503
Liver			1594			5400			7251
Lungs			398			1378			2577
Mesenteric lymph nodes			61			250			1535
Pancreas			89			77			121
Prostate			23			60			86
Rectum			8540			14571			60612
Salivary gland			29			98			227
Skeletal muscle			43			248			787
Spinal cord			31			304			243
Spleen			49			93			115
Stomach			4199			173219			248141
Subcutaneous fat			80			2624			6563
Testes			45			446			798
Thymus			47			333			814
Urinary bladder			38			833			1948

Sex	Female								
Dose level (mg/kg/day)	200			600			2000		
Lanthanum (ng/g)	max	min	median	max	min	median	max	min	median
Bone marrow			406			1281			3772
Brain			89			109			56
Colon			2542			29329			24750
Duodenum			305			11189			11364
Femur plate			380			782			3229
Femur plate marrow			342			1288			8131
Femur shaft			280			702			2511
Femur shaft marrow			64			817			2856
Heart			77			70			455

Sex	Female								
Dose level (mg/kg/day)	200			600			2000		
Lanthanum (ng/g)	max	min	median	max	min	median	max	min	median
Kidney			235			405			659
Liver			1553			3449			11050
Lungs			423			1335			3998
Mesenteric lymph nodes			71			810			1371
Pancreas			<21			108			175
Rectum			43859			10542			35097
Salivary gland			42			120			171
Skeletal muscle			110			188			905
Spinal cord			68			198			313
Spleen			38			146			86
Stomach			15046			118291			348949
Subcutaneous fat			103			183			1102
Thymus			185			556			197
Urinary bladder			65			860			374
Uterus			1411			532			3869

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Study Title: 4 Week Intravenous (Slow Bolus) Toxicity and Tissue Distribution Study in the Dog

Location of Report: Vol 21, page 001

Study Number: SPD0104

Report Status: Final

Study Initiation Date: 31 July, 2000

Study Facility:

GLP Compliance: Yes

Animals: Male and Female Beagle Dogs

Body Weights: male, 9.4-11.2 kg; female, 9.3-11.0 kg

Number/Sex/Dose: 3

Age at Initiation of Dosing: 5-7 months

Dogs were housed individually immediately prior to dosing and after dosing, and thereafter in pens by sex. Dogs were provided with 400 g of pelleted dog diet approximately 1 hour after dosing, and water ad libitum. Food was provided as 200 g meals approximately 1.5 hours prior to the 1st and 2nd doses of lanthanum.

Drug: Lanthanum Chloride Solution (17.66% w/v)

Lot Number: 9943967 429

Route of Administration: Intravenous

Vehicle: 0.9% NaCl solution

Dose Levels: 0, 0.003, 0.05, 1 mg lanthanum chloride/kg/day (2 ml/kg dose volume) with dose adjusted for most recent body weight

Treatment Duration: 4 weeks

Plasma and Tissue Lanthanum Levels: Venous blood samples were taken from all dogs at 2, 15 and 30 minutes, and 1, 2, 4, 8 and 24 hours after dosing on days 1 and 25 for determination of plasma lanthanum levels. Urine samples were collected for 24 hours over 8 hour time periods (0-8, 8-16, and 16-24 hours) during week 3 for determination of urinary lanthanum excretion. Tissue lanthanum levels were determined following terminal necropsy (see following tissue list).

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Tissue	Weigh	Tissues taken for lanthanum analysis	Fix	Slide Preparation	Microscopic Examination
adrenal glands	✓		✓	✓	✓
aorta		✓	✓	✓	✓
bone marrow		✓			
brain (4 levels examined)	✓	✓	✓	✓	✓
caecum		✓	✓	✓	✓
colon		✓	✓	✓	✓
duodenum		✓	✓	✓	✓
epididymides		✓	✓	✓	✓
eyes (incl. optic nerves)		✓	✓	✓	✓
femur (incl. marrow)		✓	✓	✓	✓
gall bladder			✓	✓	✓
heart	✓	✓	✓	✓	✓
ileum		✓	✓	✓	✓
injection sites			✓	✓	✓
jejunum		✓	✓	✓	✓
kidneys	✓	✓	✓	✓	✓
lacrimal glands		✓	✓	✓	✓
liver	✓	✓	✓	✓	✓

Tissue	Weigh	Tissues taken for lanthanum analysis	Fix	Slide Preparation	Microscopic Examination
lungs (incl. mainstem bronchi)	✓	✓	✓	✓	✓
mesenteric lymph node		✓	✓	✓	✓
oesophagus		✓	✓	✓	✓
ovaries	✓		✓	✓	✓
pancreas		✓	✓	✓	✓
pituitary	✓		✓	✓	✓
prostate	✓		✓	✓	✓
rectum		✓	✓	✓	✓
salivary gland (submandibular)	✓	✓	✓	✓	✓
sciatic nerve		✓	✓	✓	✓
site of mammary gland		✓	✓	✓	✓
skeletal muscle		✓	✓	✓	✓
skin		✓	✓	✓	✓
spinal cord (3 levels examined)		✓	✓	✓	✓
spleen	✓	✓	✓	✓	✓
sternum		✓	✓	✓	✓
stomach		✓	✓	✓	✓
submandibular lymph nodes		✓	✓	✓	✓
testes	✓	✓	✓	✓	✓
thymus	✓	✓	✓	✓	✓
thyroids (incl. parathyroids)	✓	✓	✓	✓	✓
tibia			✓		
tongue		✓	✓	✓	✓
trachea		✓	✓	✓	✓
urinary bladder		✓	✓	✓	✓
uterus	✓	✓	✓	✓	✓
vagina		✓	✓	✓	✓
all gross lesions		✓	✓	✓	✓

Due to their small size and consistency, samples of adrenals, gall bladder, ovaries, pituitary glands, prostate and thyroids were not taken for tissue lanthanum analysis.

Observations/Measurements: Dogs were observed daily for mortality and clinical signs. Body weights and food intake were determined weekly. All dogs were examined ophthalmoscopically prior to start of dosing, and during week 4. ECGs (leads I, II, III, aVL, aVR and aVF) monitored prior to initiation of treatment and immediately pre and post dosing during week 4 for determination of RR, PR, QRS, QT and QTcV (Van der Waters) intervals.

$$QTcV \text{ (Van der Waters)} = QT - 0.087 (RR - 1000)$$

(*Toxicol Sci* 45: 247-58, 1998)

Venous blood samples were taken from all dogs pretreatment and during week 4 of treatment for evaluation of hematology and clinical chemistry values.

Hematology: Hb, RBC, PVC, MCV, MCH, platelet, WBC (differential leukocyte counts), reticulocytes

Clinical Chemistry: BUN, creatinine, glucose, ALP, ALT, AST, total protein, albumin, globulins (alpha-1, alpha-2, beta and gamma), albumin/globulin ratio, bilirubin, cholesterol, triglycerides, calcium, inorganic phosphate, sodium, potassium, chloride, prothrombin time, fibrinogen, activated partial thromboplastin time.

Urinalysis: volume, glucose, bilirubin, ketones, blood pigments, pH, protein, urobilinogen, nitrites, leukocytes, erythrocytes, crystals, debris, casts, epithelial, color, appearance, sodium, potassium, chloride.

Dogs were sacrificed after 4 weeks of drug treatment, tissues removed, and examined macroscopically and microscopically (see previous tissue list, under tissue lanthanum levels).

Results

Platelet counts were considerably lower than concurrent control during week 4 in one male and one female dog given 1.0 mg lanthanum chloride/kg/day, i.v. Individual platelet counts in male and female dogs given 1 mg/kg/day, i.v. for 4 weeks were 156, 411 and 391 X 10³/μL and 598, 447 and 127 X 10³/μL, respectively. Mean platelet counts were not drug-related.

Gender	Mean (± SD) Platelet Counts (x 10 ³ /μL)			
	Intravenous Dose (mg/kg/day)			
	0	0.003	0.05	1.0
Male	351±101	388±24	392±59	319±142
Female	399±35	349±66	365±46	391±241

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There were no drug-related effects on ECG variables, including QT and QTcV intervals.

Electrocardiograms - group mean values - Pre-treatment

Group	:	1	2	3	4
Test article	:	Control	Lanthanum chloride		
Dose (mg/kg/day)	:	0	0.003	0.05	1.0

Group/sex		Heart Rate (beats/min)	R-R (secs)	P-R (secs)	QRS (secs)	Q-T (secs)	QTcV (msec)
1M	mean	119	0.51	0.12	0.03	0.19	235.7
	S.D.	17	0.08	0.02	0.01	0.01	7.0
	N	3	3	3	3	3	3
2M	mean	120	0.51	0.12	0.03	0.22	262.6
	S.D.	20	0.09	0.00	0.01	0.02	12.6
	N	3	3	3	3	3	3
3M	mean	133	0.45	0.12	0.04	0.21	257.6
	S.D.	9	0.03	0.00	0.00	0.01	7.5
	N	3	3	3	3	3	3
4M	mean	121	0.5	0.12	0.04	0.21	256.8
	S.D.	16	0.07	0.00	0.00	0.01	10.0
	N	3	3	3	3	3	3
1F	mean	124	0.49	0.12	0.037	0.21	251.3
	S.D.	13	0.06	0.00	0.01	0.01	11.2
	N	3	3	3	3	3	3
2F	mean	135	0.46	0.11	0.04	0.20	247.3
	S.D.	25	0.09	0.02	0.01	0.02	12.9
	N	3	3	3	3	3	3
3F	mean	135	0.46	0.13	0.04	0.20	250.6
	S.D.	26	0.10	0.01	0	0	7.7
	N	3	3	3	3	3	3
4F	mean	137	0.43	0.12	0.03	0.2	249.9
	S.D.	19	0.04	0.02	0.01	0.00	3.5
	N	3	3	3	3	3	3

Electrocardiograms - group mean values - Day 30

Group	:	1	2	3	4
Test article	:	Control	Lanthanum chloride		
Dose (mg/kg/day)	:	0	0.003	0.05	1.0
PREDOSE					

Group/sex	Heart Rate (beats/min)	R-R (secs)	P-R (secs)	QRS (secs)	Q-T (secs)	QTcV (msec)
1M	mean 112	0.55	0.13	0.04	0.19	233
	S.D. 19	0.11	0.01	0.00	0.01	13
	N 3	3	3	3	3	3
2M	mean 122	0.49	0.13	0.03	0.22	264
	S.D. 7	0.03	0.01	0.01	0.02	18
	N 3	3	3	3	3	3
3M	mean 128	0.47	0.11	0.03	0.20	243
	S.D. 6	0.02	0.01	0.01	0.01	8
	N 3	3	3	3	3	3
4M	mean 107	0.57	0.11	0.02	0.22	254
	S.D. 11	0.06	0.02	0.01	0.01	10
	N 3	3	3	3	3	3
1F	mean 127	0.47	0.12	0.03	0.20	243
	S.D. 5	0.02	0.01	0.01	0.01	5
	N 3	3	3	3	3	3
2F	mean 118	0.51	0.13	0.03	0.21	252
	S.D. 15	0.07	0.01	0.00	0.01	9
	N 3	3	3	3	3	3
3F	mean 136	0.44	0.13	0.04	0.20	245
	S.D. 14	0.05	0.01	0.00	0.01	7
	N 3	3	3	3	3	3
4F	mean 143	0.43	0.12	0.03	0.19	236
	S.D. 29	0.08	0.01	0.01	0.03	18
	N 3	3	3	3	3	3

Electrocardiogram - group mean values - Day 30

Group	:	1	2	3	4
Test article	:	Control	Lanthanum chloride		
Dose (mg/kg/day)	:	0	0.003	0.05	1.0
Immediately post-dose					

Group/sex		Heart Rate (beats/min)	R-R (secs)	P-R (secs)	QRS (secs)	Q-T (secs)	QTcV (msec)
1M	mean	123	0.50	0.12	0.04	0.20	247.1
	S.D.	18	0.08	0.01	0.00	0.02	27.6
	N	3	3	3	3	3	3
2M	mean	122	0.49	0.12	0.03	0.22	260.7
	S.D.	7	0.03	0.02	0.01	0.02	19.2
	N	3	3	3	3	3	3
3M	mean	124	0.48	0.11	0.03	0.20	241.6
	S.D.	8	0.03	0.01	0.01	0.01	3.4
	N	3	3	3	3	3	3
4M	mean	109	0.55	0.11	0.03	0.21	252.2
	S.D.	11	0.06	0.02	0.01	0.01	6.8
	N	3	3	3	3	3	3
1F	mean	127	0.47	0.12	0.03	0.20	249.2
	S.D.	3	0.01	0.01	0.00	0.02	15.1
	N	3	3	3	3	3	3
2F	mean	138	0.44	0.13	0.03	0.20	249.0
	S.D.	7	0.02	0.01	0.00	0.00	1.8
	N	3	3	3	3	3	3
3F	mean	134	0.45	0.13	0.04	0.20	251.2
	S.D.	11	0.04	0.01	0.00	0.02	17.7
	N	3	3	3	3	3	3
4F	mean	141	0.43	0.11	0.03	0.18	232.6
	S.D.	20	0.07	0.01	0.01	0.02	26.5
	N	3	3	3	3	3	3

The following drug-related findings are shown in the sponsor's summary table.

Fibrinogen levels during week 4 were higher than concurrent control in male and female dogs given 1 mg/kg/day.

At week 4, liver enzymes (ALT, AST, ALP), total protein, globulins, albumin/globulin ratio and triglycerides were higher than concurrent control, and inorganic phosphate was lower than concurrent control in male and female dogs given 1 mg/kg/day.

Histopathologic evidence of chronic hepatitis was present in all male and all female dogs given 1 mg/kg/day. Focal necrosis of the liver was observed in 1 female dog given 1 mg/kg/day.

Plasma lanthanum exposures (C_{max} , AUC) were dose-related, and increased more than dose proportionally. Median plasma levels at C_{max} in male and female dogs given 1 mg/kg/day for 25 days were 16,861 ng/ml (0.12 mM) and 22,065 ng/ml (0.16 mM), respectively. In female dogs, plasma lanthanum levels were higher on day 25 than on day 1. On day 25, plasma lanthanum levels in female dogs were higher than those in male dogs.

Tissue lanthanum levels were dose-related and highest in liver, spleen, gastrointestinal tract, bone and mesenteric lymph nodes (see table below). Liver and spleen lanthanum levels were considerably higher than plasma levels at C_{max} . Median liver lanthanum levels in male and female dogs given 1 mg/kg/day, iv for 25 days were 452647 (3.2 mM) and 407958 ng/g (2.9 mM), respectively (see following table).

Median tissue concentration ($\mu\text{g/g}$ wet weight)	Tissue
Dose level	0.003 mg/kg/day
Below LLoQ or upto 0.1 $\mu\text{g/g}$	Aorta, Brain (cerebellum), Brain (cerebrum), Brain (mid), Caecum, Colon, Duodenum, Epididymides, Eyes, Heart, Ileum, Jejunum, Kidneys, Lacrimal glands, Lungs, Mesenteric LN, Oesophagus, Pancreas, Rectum, Salivary Gland, Sciatic Nerve, Skeletal Muscle, Skin, Spleen, Spinal Cord, Stomach-corpus, Stomach-fundus, Stomach-pylorus, Sternum (M), Submandibular LN, Teeth, Testes, Thymus, Tongue, Trachea, Urinary Bladder, Uterus, Vagina
>0.1 to 1 $\mu\text{g/g}$	Femur, Femur-growth plate, Liver, Sternum (F)
Dose level	0.05 mg/kg/day
Below LLoQ or upto 0.1 $\mu\text{g/g}$	Brain (cerebellum), Brain (cerebrum), Brain (mid), Caecum, Epididymides, Oesophagus, Pancreas (F), Sciatic Nerve, Skeletal Muscle, Skin, Spinal Cord, Teeth, Testes (M), Thymus, Tongue, Urinary Bladder (M), Uterus, Vagina
>0.1 to 1 $\mu\text{g/g}$	Aorta, Colon, Duodenum, Eyes, Heart, Ileum, Jejunum, Kidneys, Lacrimal gland, Lungs, Mesenteric LN, Pancreas (M), Salivary Gland, Sternum Stomach-fundus, Stomach-pylorus, Rectum, Trachea, Urinary Bladder (F)
>1 to 10 $\mu\text{g/g}$	Femur, Femur-growth plate, Spleen, Stomach-corpus, Submandibular LN
>10 to 100 $\mu\text{g/g}$	Liver
Dose level	1 mg/kg/day
Below LLoQ or upto 0.1 $\mu\text{g/g}$	Brain (cerebrum), Brain (mid) (M), Teeth
>0.1 to 1 $\mu\text{g/g}$	Brain (cerebellum), Brain (mid) (F), Epididymides, Eyes (M), Sciatic nerve (M), Skeletal muscle (M), Spinal cord, Sternum, Testes, Thymus (M)
>1 to 10 $\mu\text{g/g}$	Aorta, Caecum, Colon, Duodenum (M), Eyes (F), Heart, Ileum (M), Jejunum (M), Kidneys, Lacrimal glands, Lungs (M), Oesophagus, Pancreas, Rectum, Salivary glands, Sciatic nerve (F), Skeletal muscle (F), Skin, Stomach-pylorus, Submandibular LN (M), Thymus (F), Tongue, Trachea, Urinary Bladder, Uterus, Vagina
>10 to 100 $\mu\text{g/g}$	Duodenum (F), Femur, Femur growth plate, Ileum (F), Jejunum (F), Lungs (F), Mesenteric LN, Stomach-corpus, Stomach-fundus, Submandibular LN (F)
>100 to 1000 $\mu\text{g/g}$	Liver, Spleen

SUMMARY

Lanthanum Chloride: 4 Week Intravenous (Slow Bolus) Toxicity and Tissue Distribution Study in the Beagle Dog

Shire Report No: D00015-LAM-III A	Shire Reference No. : D00015-LAM-III A CRO Study No. : SPD0104		Duration of Treatment: 4 Weeks					
Species/Strain: Beagle Dog	Route: Intravenous		Necropsy Dates Terminal: 31 August to 5 September 2000					
Weight Range on Day 1 : kg Male = 9.4 - 11.2 Female = 9.3 - 11.0	Test Material: Lanthanum chloride solution (10% w/v La) [] Batch Nos.: 9943967 429		Dosing Period Dates 31 July to 4 September 2000					
Age on Day 1 : Approximately 5 - 7 months old	Vehicle: 0.9% w/v sodium chloride intravenous infusion BP		Main Testing Facility: 					
Study in Compliance with GLP Yes	Dose Volume: 2 mL/kg		Dosing Frequency: Once daily					
Data Collected: Mortality, clinical observations, body weight, food consumption, ophthalmoscopy, electrocardiography, haematology, coagulation, blood chemistry, urinalysis, toxicokinetics, organ weights, macroscopic findings, microscopic pathology and lanthanum tissue levels.								
	Male				Female			
Daily Dose (mg/kg/day)	0	0.003	0.05	1	0	0.003	0.05	1
Number of Animals:	3	3	3	3	3	3	3	3
Treatment-related findings are shown in bold.								
Number of unscheduled deaths:	0	0	0	0	0	0	0	0
Clinical Observations	There were no treatment-related clinical signs.							
Body weight Gain (g) (Weeks 1 - 5)	0.70	1.27	1.27	0.73	0.57	1.10	0.73	0.57
	Control	% Change from Control weight gain			Control	% Change from Control weight gain		
% Change from Control weight gain	0.70	81	81	4	0.57	93	28	0
Food consumption (g/animal/day)	There were no treatment-related effects.							
Ophthalmoscopy	There were no treatment-related findings.							
Electrocardiography	There were no treatment-related effects on any electrocardiogram parameters.							
Haematology								
Platelet (10^3 /ul)	One male and one female at 1 mg/kg/day had values below background ranges. (background range: males, 4-6 month, 234 - 461, 7-12 month, 160 - 389; females, 4-6 month, 208 - 462, 7 - 12 month, 196 - 426)							
Coagulation	Control	% Change from Control			Control	% Change from Control		
Fibrinogen (mg/dl)	174	14	16	52	182	-18	-16	11

% Change from control weight gain is incorrectly listed as 0.70 and 0.57 for male and females, respectively. It should be zero for both male and female control groups.

Blood chemistry									
Sex	Male				Female				
	Control	% Change from Control			Control	% Change from Control			
Daily Dose (mg/kg/day)	0	0.003	0.05	1	0	0.003	0.05	1	
Alkaline phosphatase (U/l)	292	-3	81	149	358	-27	-17	24	
Alanine transferase (U/l)	31	-6	16	71	32	-19	9	141	
Aspartate amino transferase (U/l)	30	-23	-10	117	29	-21	-14	79	
Total protein (g/dl)	5.3	2	8	11	5.8	-10	-3	-2	
Globulin (aph) (g/dl)	2.4	4	4	29	2.6	-15	-8	12	
A/G (aph) ratio	1.3	-8	-8	-31	1.2	17	17	-17	
Beta globulin (g/dl)	1.1	-9	0	36	1.1	-18	0	18	
Triglycerides (mg/dl)	23	13	39	104	35	-23	14	11	
Inorganic phosphate (mg/dl)	7.1	6	-3	-24	6.6	11	9	-9	
Urinalysis	There were no treatment-related findings.								
Toxicokinetics									
Sex	Males				Females				
Dose level (mg/kg/day)	0.003	0.05	1	0.003	0.05	1			
Day 1									
C_{max} (ng/ml)									
T_{max} (hours)	0.02	0.02	0.02	0.18	0.02	0.02			
AUC_{0-24} (ng.h/ml)	36.72	677.2	87664	33.85	1104	111004			
AUC_{0-96} (ng.h/ml)	39.12	643.2	104234	35.84	1166	181290			
$T_{1/2}$ (hours)	7.15	4.48	9.52	7.07	6.13	17.01			
Day 25									
C_{max} (ng/ml)									
T_{max} (hours)	0.10	0.02	0.02	0.02	0.02	0.02			
AUC_{0-24} (ng.h/ml)	58.74	1802	80584	57.36	2768	207722			
AUC_{0-96} (ng.h/ml)	72.27	2029	83327	75.42	3049	353376			
$T_{1/2}$ (hours)	11.46	8.21	5.89	13.61	7.40	14.04			
Organ Weights	There were no treatment-related effects.								
Macroscopic Findings	There were no treatment-related findings.								
Microscopic Findings									
Sex	Males				Females				
Dose level (mg/kg/day)	0	0.003	0.05	1	0	0.003	0.05	1	
Liver - chronic hepatitis	0	0	0	3	0	0	0	3	
Liver - focal necrosis	0	0	0	0	0	0	0	1	
Wet tissue lanthanum concentration									
Sex	Male								
Dose level (mg/kg/day)	0.003			0.05			1		
Lanthanum (ng/g)	max	min	median	max	min	median	max	min	median
Aorta			24			218			1551
Brain cerebellum			<7			11			108
Brain cerebrum			<7			<7			35
Brain mid brain			<7			6			58
Caecum			7			70			3427
Colon			19			272			3876
Duodenum			17			263			8915

Sex	Male								
	0.003			0.05			1		
	max	min	median	max	min	median	max	min	median
Lanthanum (ng/g)									
Epididymides			<7			28			416
Eyes			<7			184			997
Femur			145			1830			26028
Femur - growth plate			366			4255			45976
Heart			6			163			1518
Ileum			27			198			4498
Jejunum			7			126			8053
Kidneys			52			491			7070
Lacrimal glands			28			287			2008
Liver			679			18059			452647
Lungs			25			241			7871
Mesenteric lymph nodes			22			317			16430
Oesophagus			15			57			1670
Pancreas			<7			105			1511
Rectum			13			188			3856
Salivary glands			60			345			3521
Sciatic nerve			<7			29			618
Skeletal muscle			<7			43			478
Skin			<11			48			1490
Spinal cord			<6			25			125
Spleen			22			2637			459409
Stemum			<30			128			577
Stomach corpus			70			1164			23978
Stomach fundus			51			849			49918
Stomach pylorus			29			217			2880
Submandibular lymph nodes			31			1348			6420
Teeth			<24			27			83
Testes			<7			34			554
Thymus			<7			50			642
Tongue			<8			64			2243
Trachea			23			179			1316
Urinary bladder			11			96			1587
Sex									
Aorta			25			349			3308
Brain cerebellum			<6			16			162
Brain cerebrum			<6			<6			98
Brain mid brain			<6			8			133
Caecum			8			83			8493
Colon			24			306			6297
Duodenum			14			298			15405
Eyes			16			228			1143
Femur			162			1509			39789
Femur - growth plate			588			4792			54483

Sex	Male								
	0.003			0.05			1		
	max	min	median	max	min	median	max	min	median
Lanthanum (ng/g)									
Heart			<6			125			2769
Ileum			19			345			10532
Jejunum			9			205			15365
Kidneys			44			924			9304
Lacrimal glands			36			274			2604
Liver			928			20717			407958
Lungs			40			322			12175
Mesenteric lymph nodes			15			368			25659
Oesophagus			12			100			2934
Pancreas			<7			74			2033
Rectum			22			179			9201
Salivary glands			28			434			2293
Sciatic nerve			<7			40			1121
Skeletal muscle			<7			37			1232
Skin			<11			86			2653
Spinal cord			<6			22			163
Spleen			26			3237			394270
Sternum			199			255			777
Stomach corpus			72			1779			46778
Stomach fundus			41			529			12989
Stomach pylorus			28			270			3803
Submandibular lymph nodes			22			1167			23480
Teeth			25			38			85
Thymus			<7			67			1243
Tongue			<6			80			6356
Trachea			29			218			2104
Urinary bladder			10			147			4109
Uterus			<7			85			2778
Vagina			<7			62			4250

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Study Title: Electron Microscopy of Stomach Samples from Mouse, Rat and Beagle Dog

Location of Report: Vol 37, pg 206

Study Number: X00223-LA-III A

Report Status: Final

Study Initiation Date: 31 July 2001

Study Facility: L

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GLP Compliance: Yes

Purpose of Study: To determine the localization of lanthanum carbonate deposits within stomach samples of lanthanum carbonate-treated animals.

Experimental Procedure and Samples Evaluated

Samples of glandular or fundic stomach, previously fixed in 10% neutral buffered formalin, were taken from four control and four treated animals from each mouse, rat and beagle dog study.

Sources of Samples	Samples Examined	Control Group Animal Numbers and Sex	Treated Group Animal Numbers and Sex (Dose)
Mouse 99 week oral carcinogenicity study (SPD088: Shire Reference M00087-LAM-III E)	Glandular Stomach	2M, 3M 202F, 203F	151M, 161M 352F, 353F (1500mg/kg/day)
Rat 104 week oral carcinogenicity study (SPD087: Shire Reference R00077-LAM-III E)	Glandular Stomach	11M, 12M 306F, 307F	241M, 242M 541F, 544F (1500mg/kg/day)
Dog 52 week oral toxicity study (SPD066: Shire Reference D00088-LAM-III A)	Fundic Stomach	43M, 45M 42F, 44F	83M, 85M 84F, 86F (2000mg/kg/day)

Key: M-Male, F-Female

These samples were secondary fixed in 2% paraformaldehyde/2.5% glutaraldehyde in 0.1M sodium cacodylate buffer. After several changes of 0.1M sodium cacodylate buffer, the samples were tertiary fixed in 1% osmium tetroxide followed by three more washes in 0.1M sodium cacodylate buffer.

All processing was performed using a [redacted] microscopy tissue processor

1µm survey sections were cut and stained with toluidine blue. Silver/gold ultrathin sections of selected areas were examined using a [redacted] transmission electron microscope. Representative areas were photographed onto [redacted] film and enlarged as required.

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Results

Transmural stomach sections examined with electron microscopy showed macrophages with electron dense inclusions (or bodies) within the cytoplasm, consistent with macrophages engulfing foreign bodies or particles (likely lanthanum in this case). These electron dense inclusions were not observed in any other cell type, or in tissues from control animals. No degenerative changes were observed in macrophages that contained electron dense inclusions.

Species	Oral Dose (mg/kg/day) ^	Study Duration (Weeks)	Stomach Tissue Evaluated	Number of Animals Exhibiting Macrophages with Electron Dense Inclusions within the Cytoplasm	
				Male	Female
Mouse	1500	99	Glandular	0 of 2	2 of 2
Rat	1500	104	Glandular	1 of 2	1 of 2
Beagle Dog	2000	52	Fundic	1 of 2	2 of 2

^ mg lanthanum carbonate/kg/day

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PHARMACOKINETICS STUDIES

Study Title: *In Vitro* Protein Binding Study: Mouse, Rat, Rabbit, Dog and Human Plasma, and Human Alpha₁-Acid Glycoprotein, Transferrin, and Albumin

Location of Report: Vol 47, pg 319

Study Number: SRU 002/004649

Report Status: Final

Study Initiation Date: 19 May 1999

Study Facility: []

GLP Compliance: Yes

Drug: Lanthanum Carbonate

Lot Number: B1066-980601

Measurement of Protein Binding: Binding of lanthanum to mouse, rat, rabbit, dog and human plasma proteins; and to human albumin, human α_1 -acid glycoprotein and human transferrin was determined by ultracentrifugation (duplicate samples) over a wide range of lanthanum concentrations. Unbound (supernatant) lanthanum levels were measured using []

Percent plasma protein binding was calculated as: $100(D_t - D_u)/D_t$, where D_t represents the total concentration of lanthanum in plasma or protein solution before ultracentrifugation, and D_u represents the unbound concentration in the supernatant after ultracentrifugation.

Results

La ³⁺ Concentration (ng/ml)	Plasma Protein Binding (%)				
	Mouse	Rat	Dog	Rabbit	Human
0.1	47.4	22.5	84.4	11.5	58.5
0.5	88.8	85.2	90.2	85.6	89.3
2.5	97.6	97.5	98.2	97.3	97.9
10	99.4	99.3	99.6	99.4	99.0
50	99.8	99.9	99.9	99.9	99.3
250	99.9	>99.9	99.9	99.9	99.7

La ³⁺ Concentration (ng/ml)	Human Protein Binding (%)		
	Albumin	α_1 -acid glycoprotein	transferrin
0.1	95.3	73.3	40.0
0.5	96.8	75.5	57.4
2.5	98.7	95.0	96.9
10	99.6	98.8	99.4
50	99.9	99.8	99.7
250	99.9	99.8	>99.9

Study Title: Pharmacokinetics and Excretion Balance in the Dog Following Single Oral Administration of Lanthanum Carbonate

Location of Report: Volume 49, pg 222

Study Number: SPD/78/W

Report Status: Final

Study Initiation Date: May 1996

Study Facility: []

GLP Compliance: Yes

Animals: Male Beagle Dogs,
Body Weight Ranges: 9.0-12.65 kg
Number/Sex/Dose: 2
Age at Dosing: Not provided

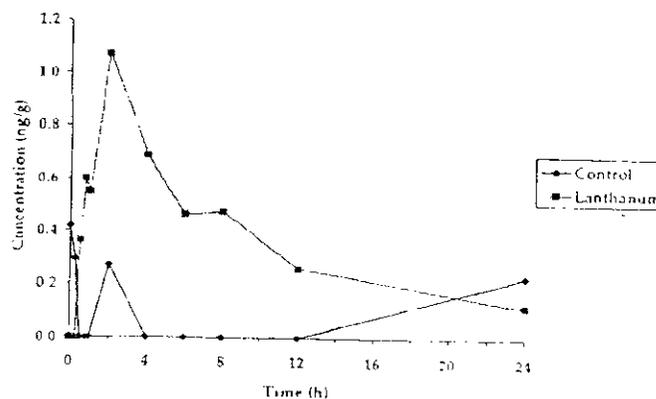
Drug: Lanthanum Carbonate
Lot Number: 6268/960101
Route of Administration: Oral administration by capsule
Positive Control Substance: Chromium oxide (6 mg/kg) in a capsule
Dose Level: 1000 mg lanthanum carbonate/kg
Treatment Duration: Single dose

Plasma drug measurements: Venous blood samples were collected at 0.25, 0.5, 0.75, 1, 2, 4, 6, 8, 12 and 24 hours after dosing

Additional Measurements: Urine and feces were collected over a 7 day post dose period, lanthanum levels measured, and percentage elimination by these routes calculated. One lanthanum treated dog (dog 310) vomited 2 hours after dosing; lanthanum concentration was determined in this vomit. Chromium oxide elimination via the fecal route was determined in control animals in order to assess methodology.

Results: Plasma lanthanum levels peaked approximately 2 hours after oral dosing.

Mean Plasma Lanthanum Concentration Time Profiles in Test and Control Group Animals



Plasma drug levels for the two lanthanum carbonate-treated dogs are shown below.

Plasma Lanthanum AUC Values for Test and Control Group Animals

Group	Dog Number	AUC _{0-24h} (ng*h/g)	Mean ± SD (ng*h/g)
Control	258 (1)	1.82	2.85 ± 1.46 (1)
Control	258 (2)	2.00	2.94 ± 1.33 (2)
Control	306	3.88	
Test	310	10.2	8.74 ± 2.07
Test	198	7.27	

(1) using 1 h concentration of <0.2 ng/g (taken as zero)

(2) using 1 h concentration of 0.29 ng/g

The percentages of lanthanum eliminated by urinary and fecal routes are shown below. Fecal elimination accounted for the majority of elimination and occurred primarily within the first 24 – 48 hours after dosing. Only a small percentage of the administered dose was eliminated renally.

Percentage Dosed Lanthanum Recovered in Urine and Faeces Following Single Oral Administration of Lanthanum Carbonate (1000 mg/kg)

Time Post-dose (h)	% Dose Recovered			
	Dog 310		Dog 198	
	Urine	Faeces	Urine	Faeces
24				
48	☐			
72				
96				
120				
144				☐
168				
Sub Totals				
Vomit				N/A
TOTAL		94.4		94.6

N/A = Not Applicable

Mean (± SD) total recovery = 94.5 ± 0.14%

The positive control substance, chromium oxide, was eliminated primarily via the fecal route, as shown below.

**Percentage Dosed Chromium Recovered in Faeces Following
Single Oral Administration of Chromium Oxide (6 mg/kg)**

Time Post-dose (h)	Dose Recovered	
	Dog 258 Faeces	Dog 306 Faeces
24		
48	[
72		
96		
120		
144		
168]
TOTAL	104.6	98.2

Mean (\pm SD) total recovery = 101.4 \pm 4.53%

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Study Title: Single Dose and 4 Week Repeat Dose Oral (Capsule) Pharmacokinetic, Tissue Distribution and Clearance Study in the Dog

Location of Report: Vol 46, page 001

Study Number: SPD0100-TK

Report Status: Final

Study Initiation Date: 25 May 2000

Study Facility:

[]

GLP Compliance: Yes

Animals: Male and female Beagle dogs

Number/sex/dose: 2 (lanthanum chloride: single dose and repeated daily dosing for 28 days)
3 (concurrent control groups; 1 and 6 month clearance groups)

Age at initiation of dosing: 5-7 months

Body weights immediately prior to dosing: M, 9.7-11.1 kg; F, 8.3-10.0 kg

Dogs were provided with 400 g standard dog chow and water ad libitum.

Drug: Lanthanum Carbonate

Lot Number: B1066-980601

Route of Administration: oral by capsule

Vehicle: none

Dose Levels: 0, 2000 mg/kg/day (daily dose given in two doses 3 hours apart)

Treatment Duration: Single daily doses on days 1 and 8 (in the same animals)

Repeated (28 days) daily doses on days 15 to 42

Clearance (1 and 6 months following 28 days of daily dosing)

Observations/Measurements: Dogs were observed daily for mortality and clinical signs. Body weights and food intake were determined weekly. At the end of dosing, dogs were sacrificed, necropsied, and tissue samples taken for determination of tissue lanthanum levels.

Blood samples were taken before and after dosing on days 1, 8, 42, 70 and 224 at the following times for plasma drug measurements.

Day 1: pre-dose, 1, 2, 3, 4 and 5 hours after the first dose (*Day 1 samples were not analyzed.*)

Day 8: pre-dose, 1, 2, 3, 4, 5, 7, 9, 12, 24, 72 hours after the first dose (*Single dose administration*)

Day 42: pre-dose, 1, 2, 3, 4, 5, 7, 9, 12, 24, 72 hours after the first dose (*28 day repeated daily dosing*)

Day 70: blood taken at approximately 9:00 am (*1 month of withdrawal*)

Day 224: blood taken at approximately 9:00 am (*6 months of withdrawal*)

The following table summarizes the animal groups, doses administered and sacrifice days. Multiple daily dosing was terminated on day 42. Days 71 and 225 represent one and six month withdrawal periods following 28 days of daily dosing.

Group number	Colour code	Number of animals		Identification numbers		Total dose level*** (mg/kg/day)	Necropsy day number
		Males	Females	Males	Females		
1	White	2	2	36, 37	52, 53	0	44
2	Blue	2	2	38, 39	54, 55	0	70*
3	Green	2	2	40, 41	56, 57	0	224**
4	Yellow	3	3	42, 43, 44	59, 60, 62†	2000	43
5	Red	2	2	45, 46	58, 61	2000	71*
6	Pink	2	2	47, 48	63, 64	2000	225**
7††	Purple	3	3	49, 50, 51	65, 66, 67	2000	NA

† Group 4 female, Number 62, euthanased on Day 41.

†† Animals in Group 7 were dosed only on Day 8. On completion of the dosing and blood sampling procedures, they were removed from this study and transferred to an unrelated study SPD0103. These animals were included in the study to obtain additional single-dose pharmacokinetic information that was uncomplicated by prior exposure to the drug. Owing to use of an incorrect feeding regimen on Day 1, toxicokinetic samples for Groups 1 to 3 from Day 1 were not analysed. Although the animals were maintained off-dose until the study restarted on Day 8, there was potential for the pharmacokinetics on this occasion to have been influenced by the prior exposure on Day 1. Data relating to this group, with the exception of the toxicokinetics data is not reported.

* Animals killed approximately 1 month after cessation of treatment

** Animals killed approximately 6 months after cessation of treatment

*** The daily dose was administered as two equal sub-doses given at least 3 hours apart.

Drug-Related Findings

Emesis occurred commonly after dosing in male and female dogs given lanthanum carbonate. The sponsor did not indicate when after dosing emesis occurred.

Group / sex	Animal number	Day numbers on which vomiting was recorded for each animal
4M	42	20, 42
	43	15, 20
	44	37, 39
5M	45	There were no incidences of vomiting in this group
	46	
6M	47	There were no incidences of vomiting in this group
	48	
4F	59	35, 37, 39, 42
	60	17, 37
	62	33, 34, 35, 36, 37, 38, 39, 40
5F	58	30
	61	27
6F	63	28, 30, 31, 34, 40
	64	42

Plasma drug levels

Plasma drug concentrations following dosing on day 8 (single dose), day 42 (28 days of repeated dosing), day 70 (one month of withdrawal) and day 224 (6 months of withdrawal) are shown below.⁴

Plasma exposure was greater following repeat daily dose administration than with a single daily dose (day 8 vs day 42), indicating accumulation occurred. Moreover, plasma lanthanum levels following 1 and 6 months of withdrawal (days 70 and 224) were similar to those observed during treatment; therefore plasma clearance was extremely slow.

Toxicokinetics - Group mean values					
Sex		Males		Females	
Total Daily Dose (mg/kg/day)		2000	2000	2000	2000
Days Dosed		1, 8, 15 - 42	8	1, 8, 15 - 42	8
Day 8	C _{max} (ng/ml)	1.29	1.48	1.5685	0.83
	T _{max} (hours)	6.14	3.67	7.57	4.00
	AUC ₀₋₂₄ (AUC _{000-24.0}) (ng.h/ml)	14.90	14.61	18.13	9.01
	AUC _{0-inf} (AUC _{inf}) (ng.h/ml)	27.58	24.34	32.68	23.47
	T _{1/2 z} (hours)	25.34	20.42	24.76	25.57
Day 42	C _{max} (ng/ml)	11.40	-	10.08	-
	T _{max} (hours)	9.14	-	4.67	-
	AUC ₀₋₂₄ (AUC _{000-24.0}) (ng.h/ml)	207.48	-	175.14	-
	AUC _{0-inf} (AUC _{inf}) (ng.h/ml)	NC	-	NC	-
	T _{1/2 z} (hours)	NC	-	NC	-
Day 70	Mean plasma level (ng/ml)	5.63		5.16	
	SD	2.65		1.01	
	N	4		4	
Day 224	Mean plasma level (ng/ml)	2.24		1.82	
	SD	2.63		0.81	
	N	2		2	

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⁴ Two sets of data are shown for the single dose administration on day 8. These differ only in that the data on the left refers to dogs that were given lanthanum on day 1 as well as day 8, whereas the data on the right refers to dogs that were given lanthanum only on day 8.

Tissue Drug Levels

Tissue lanthanum levels following daily dosing for 4 weeks (day 43) and following 1 month of withdrawal (day 71) are shown in the following table. Tissue lanthanum levels were higher than plasma lanthanum levels for many tissues, indicating tissue accumulation. Moreover, tissue and plasma lanthanum levels generally remained high following 1 month of withdrawal.

Wet tissue lanthanum concentration for Day 43 compared with Day 71							
Males and Females combined							
Dose level (mg/kg/day)	2000			2000			Day 71 median as a % of Day 43 median
	Day 43 (4 weeks dosing)			Day 71 (4 weeks withdrawal)			
Lanthanum (ng/g)	max	min	median	max	min	median	
Adrenal			21			16	76
Aorta			54			32	59
Brain (cerebellum)			<16			<7	<LLoQ
Brain (cerebrum)			<11			<8	<LLoQ
Brain (mid)			<11			<8	<LLoQ
Caecum			304			240	79
Colon			390			21	5
Duodenum			4294			380	9
Epididymides			34			<7	<LLoQ
Eyes			75			18	24
Femur - growth plate			767			634	83
Femur - shaft			330			337	102
Gall bladder			22			18	82
Heart			17			<8	<LLoQ
Ileum			1012			247	24
Jejunum			60			38	63
Kidney			80			30	38
Lacrimal glands			115			25	22
Liver			1454			1058	73
Lungs			366			260	71
Mesenteric lymph nodes			549			183	33
Oesophagus			94			53	56
Ovaries			16			<9	<LLOQ
Pancreas			14			<8	<LLoQ
Pituitary			<45			<25	<LLoQ
Prostate			28			<7	<LLoQ
Rectum			12893			50	0.4
Salivary glands			51			17	33
Sciatic nerve			33			<9	<LLoQ
Skeletal muscle			44			<8	<LLoQ

Dose level (mg/kg/day)	2000			2000			Day 71 median as a % of Day 43 median
	Day 43 (4 weeks dosing)			Day 71 (4 weeks withdrawal)			
	max	min	median	max	min	median	
Lanthanum (ng/g)							
Skin			154			7117	4621
Spinal cord			69			<7	<LLoQ
Spleen			17			12	71
Stemum			40			<32	<LLoQ
Stomach corpus			57623			7174	12
Stomach fundus			8837			14477	164
Stomach pylorus			40086			13762	34
Submandibular lymph nodes			280			178	64
Teeth			8320			3344	40
Testes			156			<8	<LLoQ
Thymus			18			11	61
Thyroids			201			170	85
Tongue			21			<7	<LLoQ
Trachea			59			45	76
Urinary bladder			17			<8	<LLoQ
Uterus			19			<9	<LLoQ
Vagina			45			<7	<LLoQ

Tissue lanthanum levels following 4 weeks of dosing and 6 months following withdrawal (day 225) are shown below. Significant lanthanum levels remain even at 6 months following withdrawal.

Wet tissue lanthanum concentration for Day 43 compared with Day 225							
Males and Females combined							
Dose level (mg/kg/day)	2000			2000			Day 225 median as a % of Day 43 median
	Day 43 (4 weeks dosing)			Day 225 (26 weeks withdrawal)			
	max	min	median	max	min	median	
Lanthanum (ng/g)							
Adrenal			21			18	86
Aorta			54			24	44
Brain (cerebellum)			<16			<6	<LLoQ
Brain (cerebrum)			<11			<7	<LLoQ
Brain (mid)			<11			<7	<LLoQ
Caecum			304			72	24
Colon			390			8	2
Duodenum			4294			22	0.5
Epididymides			34			<6	<LLoQ
Eyes			75			13	17
Femur - growth plate			767			664	87
Femur - shaft			330			167	51
Gall bladder			22			12	55
Heart			17			<7	<LLoQ
Ileum			1012			165	16
Jejunum			60			16	27

Dose level (mg/kg/day)	2000			2000			Day 225 median as a % of Day 43 median
	Day 43 (4 weeks dosing)			Day 225 (26 weeks withdrawal)			
Lanthanum (ng/g)	max	min	median	max	min	median	
Kidney			80			22	28
Lacrimal glands			115			13	11
Liver			1454			1196	82
Lungs			366			126	34
Mesenteric lymph nodes			549			70	13
Oesophagus			94			30	32
Ovaries			16			8	50
Pancreas			14			<7	<LLoQ
Pituitary			<45			<23	<LLoQ
Prostate			28			16	57
Rectum			12893			33	0.3
Salivary glands			51			11	22
Sciatic nerve			33			<7	<LLoQ
Skeletal muscle			44			<6	<LLoQ
Skin			154			27	18
Spinal cord			69			<7	<LLoQ
Spleen			17			10	59
Stemum			40			396	990
Stomach corpus			57623			12811	22
Stomach fundus			8837			4750	54
Stomach pylorus			40086			11548	29
Submandibular lymph nodes			280			96	34
Teeth			8320			2430	29
Testes			156			<6	<LLoQ
Thymus			18			26	144
Thyroids			201			68	34
Tongue			21			<7	<LLoQ
Trachea			59			32	54
Urinary bladder			17			<7	<LLoQ
Uterus			19			<7	<LLoQ
Vagina			45			<7	<LLoQ

The following table shows tissue lanthanum levels to be highest in gastrointestinal tract, liver, teeth and bone. Lanthanum levels up to 10,000 times those seen in plasma were observed in these tissues. Intermediate tissue levels (10-100 times plasma levels) were seen in other portions of the gastrointestinal tract, bone, lungs, skin spinal cord, testes, submandibular lymph node, and thyroid.

Median tissue concentration (µg/g wet weight)	Tissue			
LLoQ or upto 0.1µg/g	Adrenals	Gall Bladder	Prostate	Tongue
	Aorta	Heart	Salivary Gland	Trachea
	Brain (cerebellum)	Jejunum	Sciatic Nerve	Urinary Bladder
	Brain (cerebrum)	Kidney	Skeletal Muscle	Uterus
	Brain (mid)	Oesophagus(M)	Spleen	Vagina
	Caecum (F)	Ovaries	Spinal Cord (F)	
	Epididymides	Pancreas	Sternum	
	Eyes	Pituitary	Thymus	
>0.1 to 1µg/g	Caecum (M)	Ileum (M)	Skin	Thyroids
	Colon	Lacrimal gland	Spinal Cord (M)	
	Femur-growth plate	Lungs	Submandibular LN	
	Femur-shaft	Mesentenc LN	Testes	
>1 to 10 µg/g	Duodenum	Liver	Rectum (F)	Teeth
	Ileum (F)	Oesophagus(F)	Stomach-fundus(M)	
>10 to 100 µg/g	Rectum (M)	Stomach-corporus	Stomach-fundus(F)	Stomach-pylorus

Lanthanum washed out from tissues extremely slowly. At 1 and 6 months following treatment cessation, significant lanthanum concentrations were observed in several tissues, particularly bone, skin, stomach fundus, liver, lungs, femur growth plate, submandibular lymph node, and thyroid. Comparison of 1 and 6 month data shows clearance to be slowest for bone, femur growth plate, stomach and liver.

1 Month Withdrawal

Tissue concentration after 4 weeks off dose (as % of median concentration at end of dosing)	Tissue			
<1%	Rectum			
1 to <10%	Colon	Duodenum		
10 to <50%	Ileum	Lacrimal Glands	Mesenteric LN	Stomach-corporus
	Stomach-pylorus	Teeth		
50 to <100%	Caecum	Femur-growth plate	Liver	Lungs
	Submandibular LN	Thyroids		
100% or greater	Femur-shaft	Skin	Stomach-fundus	

Six Month Withdrawal

Tissue concentration after 4 weeks off dose (as % of median concentration at end of dosing)	Tissue			
<1%	Duodenum	Rectum		
1 to <10%	Colon			
10 to <50%	Caecum	Lungs	Mesenteric LN	Ileum
	Stomach-pylorus	Submandibular LN	Skin	Lacrimal Glands
	Teeth	Thyroids	Stomach-corporus	
50 to <100%	Femur-shaft	Femur-growth plate	Liver	Stomach-fundus
100% or greater				

1 Month Withdrawal vs 6 Months of Withdrawal

Tissue concentration after 4 weeks off dose (as % of median concentration at end of dosing)	Tissue			
	4 Weeks Withdrawal		26 Weeks Withdrawal	
<1%	Rectum		Duodenum	Rectum
1 to <10%	Colon	Duodenum	Colon	
10 to <50%	Ileum Mesenteric LN Stomach-pylorus	Lacrimal Glands Stomach-corporus Teeth	Caecum Stomach-pylorus Teeth Mesenteric LN Lacrimal Glands	Lungs Submandibular LN Thyroids Ileum Stomach-corporus skin
50 to <100%	Caecum Liver Submandibular LN	Femur-growth plate Lungs Thyroids	Femur-shaft Liver	Femur-growth plate Stomach-fundus
100% or greater	Femur-shaft Stomach-fundus	Skin		

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/s/

John Koerner
12/4/02 05:16:25 PM
PHARMACOLOGIST

You signed off on this review in December.

Charles Resnick
12/4/02 05:33:05 PM
PHARMACOLOGIST