CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-127

PHARMACOLOGY REVIEW(S)

NDA 22-127

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA

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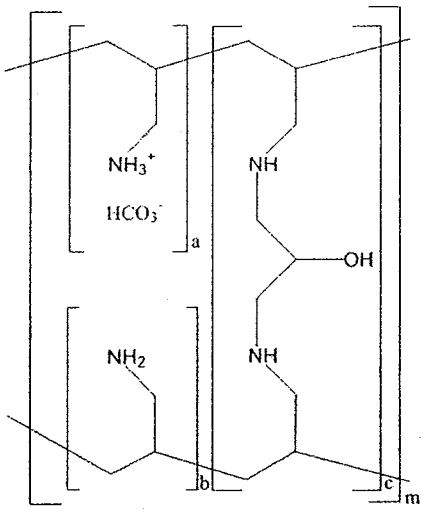
August 8, 2007

ORIGINAL NDA DATED: December 20, 2006
CENTER RECEIPT DATE: December 20, 2006
REVIEWER RECEIPT DATE: January 3, 2007

SPONSOR: Genzyme Corporation
500 Kendall Street
Cambridge, MA 02142

DRUG: Trade name - Renvela™ Tablets
Generic name – Sevelamer carbonate
Code name – GT335-012

Chemical Structure of Sevelamer Carbonate



Where:
a, b = number of primary amine groups a + b = 9
c = number of crosslinking groups c = 1
m = large number to indicate extended polymer network

FORMULATION: Renvela tablets are formulated to contain 800 mg anhydrous sevelamer carbonate. Inactive ingredients include microcrystalline cellulose, sodium

chloride and zinc stearate.

PHARMACOLOGICAL CLASS: Phosphate binder

PROPOSED INDICATION: For controlling serum phosphorus levels in chronic kidney disease (CKD) patients on dialysis.

PROPOSED DOSAGE REGIMEN: The recommended starting dose of Renvela is 2.4 to 4.8 g/day which can be administered as one to two 800 mg tablets three times per day with meals based on serum phosphorus level. The dose should be titrated up or down by one tablet per meal at two week intervals, as needed, to control the serum phosphorus levels within the target range of 3.5 to 5.5 mg/dL. (In a cross-over trial comparing sevelamer carbonate and sevelamer hydrochloride, the average daily dose of both carbonate and hydrochloride was found to be 6 g/day. The highest daily dose of sevelamer carbonate studied was 14 g in CKD patients on dialysis)

IND UNDER WHICH CLINICAL TRIALS WERE CONDUCTED: IND 66,710

RELATED NDAs: NDA 20-926 – Renagel Capsules (sevelamer hydrochloride) and NDA 21-179 – Renagel Tablets (sevelamer hydrochloride)

EXECUTIVE SUMMARY

Background

Renvela™ (sevelamer carbonate), a non-absorbed phosphate-binding polymer, has been developed as an alternative to the currently marketed sevelamer hydrochloride (Renagel®, NDAs 20-926 and 21-179), for the control of serum phosphorus in chronic kidney disease (CKD) patients on hemodialysis.

Both carbonate and hydrochloride salt forms of sevelamer are polymeric anion exchange resins. Although the counterions differ, the polymer itself (the active moiety responsible for binding of phosphate) is the same for both compounds. Thus, both salts are expected to have equivalent phosphate binding activities. The carbonate salt of sevelamer has been developed to avoid the hyperchloremia that has been associated with the use of the currently approved sevelamer hydrochloride in some patients. The hyperchloremia and hence the reduction of serum bicarbonate levels are expected to be minimized with the use of the carbonate salt of sevelamer. Renagel® (sevelamer hydrochloride) has a labeled precaution that serum chloride and serum bicarbonate levels should be monitored during treatment. Replacement of the chloride counterion with carbonate is intended to preclude the need for frequent monitoring of the above parameters.

Sevelamer carbonate is a highly cross-linked poly (allylamine) polymer that contains multiple amines which become protonated in the stomach (and thus positively charged) and bind negatively charged dietary phosphate ions. Phosphate sequestered in the polymer is not absorbed from the GI tract and is excreted in the feces, thus reducing the serum phosphorus levels in CKD patients on dialysis.

Proposed labeling for Renvela recommends a starting dose of 2.4 to 4.8 g/day which can be administered as one to two 800 mg tablets three times a day with meals based on serum phosphorus level. The dose is titrated up or down every two weeks, if needed, for controlling the serum phosphorus levels within the target range of 3.5 to 5.5 mg/dL.

I. Recommendations

A. Recommendation on Approvability

Renvela™ is approvable from a nonclinical perspective.

B. Recommendations for Nonclinical Studies

None

C. Recommendations on Labeling

1. Sponsor's proposed text under section **8. USE IN SPECIFIC POPULATIONS, 8.1. Pregnancy** presently reads as follows:

We recommend that the above text be revised to read as follows:

2. Under section **13. NONCLINICAL TOXICOLOGY, 13.1. Carcinogenesis, Mutagenesis, Impairment of Fertility,** sponsor's proposed text presently reads as follows:

[ ]

We recommend that the above text be revised to read as follows:

Standard lifetime carcinogenicity bioassays were conducted in mice and rats. Rats were given sevelamer hydrochloride by diet at 0.3, 1 or 3 g/kg/day. There was an increased incidence of urinary bladder transitional cell papilloma in male rats of the high dose group (human equivalent dose twice the maximum clinical trial dose of 13 g). Mice received dietary administration of sevelamer hydrochloride at doses of up to 9 g/kg/day (human equivalent dose 3 times the maximum clinical trial dose). There was no increased incidence of tumors observed in mice.

In an in vitro mammalian cytogenetic test with metabolic activation, sevelamer hydrochloride caused a statistically significant increase in the number of structural chromosome aberrations. Sevelamer hydrochloride was not mutagenic in the Ames bacterial mutation assay.

Sevelamer hydrochloride did not impair the fertility of male or female rats in a dietary administration study in which the females were treated from 14 days prior to mating through gestation and the males were treated for 28 days prior to mating. The highest dose in this study was 4.5 g/kg/day (human equivalent dose 3 times the maximum clinical trial dose of 13 g).

II. Summary of Nonclinical Findings

Nonclinical studies conducted with sevelamer carbonate included *in vitro* binding studies, a 28-day pharmacokinetic and mass balance study in dogs using radiolabeled drug, and 4-week oral toxicity studies in rats and dogs.

In vitro binding studies showed that the phosphate binding *capacity* constants were similar for the carbonate and hydrochloride salts with and without acid pre-treatment (acid treatment is intended to simulate the acidic environment of the stomach). The binding *affinity* constant for the carbonate salt, before acid-pretreatment, was lower than the value for the hydrochloride salt; however, the values for both salts were mostly similar following acidification.

In the 28-day pharmacokinetic study, male and female dogs were dosed orally (capsule) with ^{14}C sevelamer carbonate on days 1 and 28 (200 mg/kg/day; radioactivity = 1.85MBq/kg) and non-radiolabeled drug on days 2 to 27. Blood, urine and fecal samples were collected on days 1 and 28 for radioactivity measurements. Results of the study indicated that more than 94% of the radioactivity was excreted in the feces within the first 24 hours post-dose. Only 0.04 – 0.07% of the dose of the radioactivity was recovered

in urine, indicating negligible absorption. The plasma radioactivity levels were non-quantifiable on both days 1 and 28 and the levels found in the bile were negligible (0.0002-0.0003% of the dose). Because of the apparently negligible levels of absorption, drug levels in tissues were not determined.

Four-week oral toxicity studies in rats and dogs compared the toxicity profiles of the carbonate and hydrochloride salts of sevelamer. Groups of Sprague-Dawley rats were given dietary administration of sevelamer carbonate or hydrochloride at dose levels of 1000 or 4500 mg/kg/day. The control group received dietary administration of methylcellulose at 4500 mg/kg/day. Both carbonate and hydrochloride salts, at the high dose (4500 mg/kg/day), produced reduced serum vitamin E levels. No drug-related findings were noted in organ weights or macroscopic and histopathologic parameters. Except for the expected increased urinary excretion of chloride in the high dose sevelamer hydrochloride treated animals, clinical chemistry and urinary parameters were similar for both salts. The NOAEL for both sevelamer salts was 1000 mg/kg/day.

In the dog study, oral (capsule) administration of sevelamer carbonate or hydrochloride at 200 and 1000 mg/kg/day for 4 weeks, produced dose-related, statistically nonsignificant, decreases in serum vitamin E and D levels (for both salt forms), when compared to pretreatment levels. There were no other drug-related findings in dogs. A NOAEL was not established in dogs.

The above toxicity studies in rats and dogs revealed similar toxicity profiles for sevelamer carbonate and sevelamer hydrochloride (Renagel®). Though no systemic toxicity was observed, reduced serum levels of fat soluble vitamins were seen with the administration of both salts. These findings are consistent with those seen in earlier studies with Renagel®. The earlier studies also showed that sevelamer hydrochloride binds to bile acids; the inhibition of bile acid absorption could cause reduced absorption of fat and fat soluble vitamins (A, D, E and K). Though large quantities of vitamins A, D and E are usually stored in the body, this is not true of vitamin K. It is known that vitamin K deficiency could lead to decreased formation of several important blood clotting factors (prothrombin, and factors VII, IX and X), thus resulting in serious impairment of blood coagulation. Increased incidences of mortalities and hemorrhages in various organs were observed in several rat toxicity studies conducted with sevelamer hydrochloride at 10 g/kg/day. Prothrombin time and activated partial thromboplastin time were increased in these studies. Charles River CD rats were found to be more sensitive to hemorrhagic effects than Harlan SD rats.

Labeling for Renagel® states that "in preclinical studies in rats and dogs, sevelamer hydrochloride reduced vitamin D, E, K and folic acid levels at doses of 6-100 times the recommended human dose. In clinical trials, there was no evidence of reduction in serum levels of vitamins with the exception of a one year clinical trial in which Renagel treatment was associated with reduction of 25-hydroxyvitamin D." Vitamin supplements are generally provided to hemodialysis patients.

Acute and chronic toxicity, reproductive and developmental toxicology, genotoxicity and carcinogenicity studies conducted with sevelamer hydrochloride were previously reviewed by the agency during the NDA approval process for that drug.

Renagel® has been approved in the United States since 1998, and is currently approved in over 50 countries. According to the sponsor, it is estimated that approximately ——— patients worldwide have been exposed to sevelamer hydrochloride. The most common treatment-related adverse events include vomiting, nausea, dyspepsia, diarrhea, abdominal pain and flatulence. In a cross-over study in hemodialysis patients, the adverse events observed with sevelamer carbonate were similar to those reported for sevelamer hydrochloride.

Since the non-clinical data indicate that the toxicity profiles for sevelamer carbonate and sevelamer hydrochloride (Renagel®) are similar, and as sevelamer carbonate is intended to be used in the same patient population at similar dosage levels as Renagel®, there are no approvability issues for sevelamer carbonate from the nonclinical toxicity testing program perspective.

Reviewer Signature: _____

Supervisor Signature: Concurrence _____
Charles A. Resnick, Ph.D.

PHARMACOLOGY/TOXICOLOGY REVIEW

Renvela™ (sevelamer carbonate) has been developed as a pharmaceutical alternative to the currently marketed product, Renagel® (sevelamer hydrochloride). Both carbonate and hydrochloride salt forms of sevelamer are polymeric anion exchange resins. Although the counterions differ, the polymer itself (the active moiety responsible for binding of phosphate) is the same for both compounds. Nonclinical studies conducted with sevelamer hydrochloride were reviewed under NDAs 20-926 (for capsules) and 21-179 (for tablets). The sponsor refers to sevelamer hydrochloride studies to support the approval of sevelamer carbonate since cross-reference to approved NDAs for sevelamer hydrochloride was agreed to by the agency in its response (dated April 14, 2003) to the sponsor's Pre-IND meeting package. Studies conducted with sevelamer carbonate to bridge from the existing pharmacokinetic and toxicology data for the hydrochloride salt of sevelamer to the carbonate salt include: in vitro binding studies, a 28-day multi-dose radio-labeled ADME study in dogs, and 4-week oral toxicity studies in rats and dogs. These studies were reviewed under IND 66,710 by Dr. Ronald Wange of the Division of Metabolism and Endocrinology Products (Pharmacology/Toxicology Review dated 1/28/2005). Dr.Wange's review is provided below.

2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary: The active component of Renagel® (sevelamer hydrochloride), Allylamine polymer with 1-chloro-2,3-epoxypropane, is only minimally absorbed from the gastrointestinal tract, and acts by binding and sequestering dietary phosphate, thereby inhibiting intestinal absorption of phosphate. Sevelamer carbonate shares the same active component, and *in vitro* equilibrium studies indicate that the carbonate salt has a similar phosphate binding capacity constant as Renagel®. However, the carbonate salt also has a lower phosphate binding affinity constant, suggesting that the carbonate counterion may partially compete with phosphate for binding to sevelamer. This difference is less apparent following acidification, suggesting that the two agents may possess more similar phosphate binding characteristics after being processed through the acidic environment of the stomach.

2.6.2.2 Primary pharmacodynamics

In vitro binding studies:

Study title: Equilibrium Study of Binding of Phosphate to Sevelamer Carbonate and Sevelamer Hydrochloride 800 mg Tablets Without Acid Pre-treatment

The phosphate binding affinity constant, k_1, and phosphate binding capacity constant, k_2, were experimentally determined for both sevelamer carbonate and sevelamer hydrochloride at pH 7.0 by generation of a saturation binding isotherm and linear transformation by Langmuir plot. Sevelamer carbonate showed a significantly lower binding affinity constant (0.374) as compared to sevelamer hydrochloride (0.863). However, the binding capacity constant was comparable for both agents: 5.97 for sevelamer carbonate and 5.89 for sevelamer hydrochloride.

Study title: Equilibrium Study of Phosphate Binding to Sevelamer Carbonate and Sevelamer Hydrochloride 800 mg Tablets with Acid Pre-treatment

As above, except that both agents were first pre-treated with hydrochloric acid prior to determination of the phosphate binding parameters. Acid pre-treatment reduced the gap in the value for the phosphate binding affinity constant: 0.688 for sevelamer carbonate and 0.820 for sevelamer hydrochloride. The binding capacity constants were again comparable: 6.58 for sevelamer carbonate and 6.23 for sevelamer hydrochloride.

Study title: Kinetic Study of Phosphate Binding

The carbonate and chloride (Renagel®) salts of sevelamer were compared in terms of the amount of phosphate bound over time under conditions of 2.5 mM phosphate and 38.7 mM phosphate. Both agents exhibited fast binding, reaching equilibrium in approximately 10 minutes. However, the carbonate salt of sevelamer bound less

phosphate at equilibrium. This was especially pronounced at the lower phosphate concentration (2.5 mM), giving equilibrium binding values at 30 min of 85% for sevelamer carbonate and 95% for Renagel®.

Mechanism of action:

Prevents absorption of phosphate from the gastrointestinal tract

2.6.2.4 Safety pharmacology

See original review for NDA 20-926

2.6.2.5 Pharmacodynamic drug interactions

See original review for NDA 20-926

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

2.6.4.1 Brief summary

Sevelamer carbonate shows ADME characteristics that are comparable to those previously reported for Renagel® (see original review of NDA 20-926). Plasma levels were non-quantifiable, and greater than 94% of radiolabeled drug was eliminated in feces. Less than 0.1% of the isotope could be recovered in urine. Given the apparently low levels of absorption, drug levels in tissues and other pharmacokinetic parameters were not evaluated.

2.6.4.2 Methods of Analysis

Study title: Plasma Pharmacokinetics, Excretion Balance and Tissue Distribution of Radioactivity Following Repeated Oral Administration to Dogs for 28 Days

Key study findings: Sevelamer carbonate shows the same ADME characteristics as sevelamer hydrochloride (NDA 20-926).

Study no.: GT-153-PK-1 (25117 PSC)
Volume #2, and page #1:
Conducting laboratory and location:

[redacted]

Date of study initiation: 25 June 2003
GLP compliance: yes
QA report: yes (x) no ( )

Drug	**lot #**	**% purity**:
Sevelamer carbonate		
^{14}C-labeled	CSL-03-006-13-25	[redacted]
Unlabeled	X2365915	na

Methods

Doses:
200 mg/kg/day
^{14}C-radiolabeled (1.85 MBq/kg) drug on days 1 and 28
Unlabeled drug on days 2-27
Species/strain: Canine/Beagle
Number/sex/group or time point (main study): 3 male and 3 female
Route, formulation, volume, and infusion rate: Oral, capsules, 2 capsules, once daily
Satellite groups used for toxicokinetics or recovery: na
Age: approximately 8 months
Weight: mean, 8.5 kg for males, 8.4 kg for females
Sampling times:
Blood collection:
Day 1: 0, 0.25, 0.5, 1, 2, 3, 4, 6, 10 and 24 hours post-gavage
Day 28: 0, 0.25, 0.5, 1, 2, 3, 4, 6, 10, 24, 48, 72, 120 and 168 hours post-gavage
Urine, feces and cage-wash collection:
24 hour period prior to radioactive gavage on days 1 and 28
Periods of 0-24, 24-48, 48-72, 72-96, 96-120, 120-144 and 144-168h following radioactive gavage on days 1 and 28
Tissue collection (post sacrifice):
168 hours following radioactive gavage on day 28
Unique study design or methodology (if any): na

2.6.4.3 Absorption

Plasma radioactivity levels were below the quantifiable limit (3.0 Bq/gm)

2.6.4.4 Distribution

Not examined in light of non-quantifiable plasma levels.

2.6.4.5 Metabolism

Not examined in light of non-quantifiable plasma levels and ≥94% recovery of radioactivity in feces.

2.6.4.6 Excretion

96.5/94.8% (males/females) of dose recovered in feces following day one dosing, and 95.7/95.8% following day 28 dosing. 0.04/0.07% of the dose recovered in urine following day one dosing, and 0.04/0.05% following day 28 dosing. Elimination of the dose was rapid, with >94% of the dose eliminated within 24 hours of administration.

2.6.4.7 Pharmacokinetic drug interactions

Not examined.

2.6.4.8 Other Pharmacokinetic Studies

None

2.6.4.9 Discussion and Conclusions

The data indicate that the active component of sevelamer carbonate is minimally absorbed from an oral dose. While the data could be interpreted as indicating non-absorption, they are not definitive, and do not rule out inefficient absorption of sevelamer or metabolic products thereof. The data do indicate that sevelamer carbonate is similar to sevelamer hydrochloride (see NDA 20,926) in terms of overall ADME parameters.

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

In the 4-week rat study, treatment-related changes were noted in blood chemistry, blood vitamin E levels and electrolyte excretion (detailed below). With the exception of the levels of chloride in urine, sevelamer carbonate and sevelamer hydrochloride showed comparable changes. Chloride was elevated in HD sevelamer hydrochloride-treated rats (presumably as a consequence of the high dose of chloride delivered with the SH), and reduced in HD sevelamer carbonate-treated rats. The changes in blood chemistry and urinalysis were consistent with those noted for sevelamer hydrochloride (Renagel®) in NDA 20-926. In the 4-week dog study both HD sevelamer carbonate- and HD sevelamer hydrochloride-treated dogs showed less weight gain than controls and LD treatment groups and appeared more emaciated than controls. HD sevelamer carbonate- and HD sevelamer hydrochloride-treated dogs showed comparable reductions in blood levels of vitamins D and E. No other significant treatment-related effects were noted.

General toxicology: See above summary and original review for NDA 20-926

Genetic toxicology: See original review for NDA 21-179

Carcinogenicity: See original review for NDA 21-179

Reproductive toxicology: See original review for NDA 21-179

2.6.6.2 Single-dose toxicity: See original review for NDA 20-926

2.6.6.3 Repeat-dose toxicity

Study title: 4-Week Toxicity Study by Oral Route (Dietary Admixture) in Rats

Key study findings: Toxicology profile for sevelamer bicarbonate is similar to that of sevelamer hydrochloride.

Study no.: GT-153-TX-1 (24921 TSR)

Volume #2, and page #141:
Conducting laboratory and location:

[ ]

Date of study initiation: 6 February 2003
GLP compliance: yes
QA report: yes (x) no ( )
Drug, lot #, and % purity:
Sevelamer carbonate: X2365915
Sevelamer hydrochloride: 2336955

Methods

Doses:
Treatment: 1000 or 4500 mg/kg/day of either sevelamer carbonate (SC) or sevelamer hydrochloride (SH) for 28 days
Control: 4500 mg/kg/day of methylcellulose for 28 days
Species/strain:
Sprague-Dawley Rat
Number/sex/group or time point (main study):
120 (60m and 60f), 12m and 12f per group (one control, 4 treatment)
Route, formulation, volume, and infusion rate:
oral, dietary admixture, continuous
Age: Approximately 5 weeks old
Weight: mean, 162g for males and 121 g for females
Sampling times: 28 days after initiation of treatment
Unique study design or methodology (if any): none

Observation and Times: (this information can be provided in a separate section OR evaluation times can be described for each parameter in the results section).
Clinical signs: Animals checked twice daily (once daily on weekends and holidays)
Body weights: Weekly
Food consumption: Weekly
Ophthalmoscopy:
Prior to initiation of treatment period and at the end of the treatment period
EKG: na
Hematology: After completion of the treatment period
Clinical chemistry: After completion of the treatment period
Urinalysis: After completion of the treatment period
Gross pathology: After completion of the treatment period
Organ weights: After completion of the treatment period
Histopathology: After completion of the treatment period

Results:

Mortality: No unscheduled deaths

Clinical signs: No relevant clinical signs noted

Body weights: LDm on SC or SH had significantly greater body weight gain (+17 and +13%) than controls, while HDm on SC had lower body weight gain than controls.

Mean body weight and body weight gain (g)

	Males					Females				
Dose-level (mg/kg/day) Test item	0	1000 (SC)	4500 (SC)	1000 (SH)	4500 (SH)	0	1000 (SC)	4500 (SC)	1000 (SH)	4500 (SH)
Day 1	160	159	161	164	166	121	121	122	121	121
Day 29	301	324*	287	324*	304	194	195	195	197	192
Days 1-29	+141	+165	+126	+160	+138	+73	+74	+73	+76	+71
% from controls	-	*+17*	*-11*	*+13*	*-2*	-	*+1*	*0*	*+4*	*-3*

SC: Sevelamer carbonate, SH: Sevelamer hydrochloride
Statistically significant from controls, *: $p<0.05$

Food consumption: Food consumption was increased dose-dependently in SC- or SH-treated females. Males showed smaller increases in food consumption, which were not dose-dependent.

Mean food consumption (g/animal/day)

	Males					Females				
Dose-level (mg/kg/day) Test item	0	1000 (SC)	4500 (SC)	1000 (SH)	4500 (SH)	0	1000 (SC)	4500 (SC)	1000 (SH)	4500 (SH)
Days 1 to 28	23.2	23.7	23.8	24.7	25.1	16.9	17.8	19.0	17.9	19.7
% from controls	-	*+2*	*+3*	*+6*	*+8*	-	*+5*	*+12*	*+6*	*+17*

SC: Sevelamer carbonate, SH: Sevelamer hydrochloride

Ophthalmoscopy: No treatment-related changes were noted

Hematology: No treatment-related changes were noted

Clinical Chemistry:
P is elevated in all treatment groups.
HD(m/f) SC- and SH-treated animals showed elevated ALP.
HD(m/f) SC- and SH-treated animals showed reduced vitamin E.

Blood biochemical parameters

	Males					Females				
Dose-level (mg/kg/day) Test item	0	1000 (SC)	4500 (SC)	1000 (SH)	4500 (SH)	0	1000 (SC)	4500 (SC)	1000 (SH)	4500 (SH)
Sodium (mmol/L)	142.3	**143.6***	143.3	143.7	143.0	141.7	141.3	141.6	140.3	**139.2***
Potassium (mmol/L)	4.13	**3.89***	**3.85***	4.10	3.91	3.91	4.08	3.85	4.16	3.78
Chloride (mmol/L)	101.3	101.5	**102.7***	102.1	101.3	103.1	103.6	104.5	103.2	102.0
Calcium (mmol/L)	2.66	2.67	2.72	2.65	2.67	2.68	2.62	2.63	2.67	**2.59****
Inorg. phos. (mmol/L)	2.81	**3.51****	**3.35****	**3.40****	**3.37****	2.48	**2.77****	**3.40****	2.52	**2.86****
Urea (mmol/L)	6.1	**5.3***	7.4	6.0	6.8	6.5	6.7	**8.1****	6.9	**8.0****
Creatinine (µmol/L)	37	38	**41***	38	**40****	42	42	43	42	45
Cholesterol (mmol/L)	2.4	2.6	**2.6***	2.5	2.4	2.7	2.9	**3.1****	2.7	3.0
ALP (IU/L)	230	**271****	**332****	258	**309****	183	201	**242****	184	**215***
ASAT (IU/L)	48	48	**61****	50	**64****	49	53	53	50	54
ALAT (IU/L)	24	25	**36****	26	**35****	24	23	**30****	22	26

SC: Sevelamer carbonate, SH: Sevelamer hydrochloride, Inorg. phos.: inorganic phosphorus
Statistically significant from controls, *: $p<0.05$; **: $p<0.01$

Vitamins A, D and E levels

	Males					Females				
Dose-level (mg/kg/day) Test item	0	1000 (SC)	4500 (SC)	1000 (SH)	4500 (SH)	0	1000 (SC)	4500 (SC)	1000 (SH)	4500 (SH)
Vitamin A (ng/mL)	788 ± 107	879 ± 110	817 ± 137	959** ± 108	841 ± 261	494 ± 76	518 ± 56	552 ± 68	502 ± 114	548 ± 87
1:25-dihydroxyvitamin D (pg/mL)	253.9 ± 48.7	292.6 ± 53.1	305.6 ± 60.2	274.0 ± 63.0	305.2 ± 76.3	141.8 ± 44.5	118.4 ± 50.7	243.5** ± 58.1	112.3 ± 37.3	197.6* ± 66.4
Vitamin E (µg/mL)	3.89 ± 0.48	3.94 ± 0.18	1.25** ± 1.21	4.19 ± 0.33	0.82** ± 1.14	6.09 ± 1.11	6.57 ± 0.68	4.21** ± 0.71	5.99 ± 0.54	4.64** ± 0.64

SC: Sevelamer carbonate, SH: Sevelamer hydrochloride
Statistically significant from controls, *: $p<0.05$, **: $p<0.01$

Urinalysis:

Alkalinization of urine was noted in SH-treated males and LD SC-treated males.
Na was reduced in all treatment groups. Effect was not dose-dependent.
SC-treated animals showed reduced Cl excretion, while HD(m/f) SH-treated animals had elevated Cl excretion.
Increased Ca^{2+} excretion in HD(m/f) SC- and SH-treated animals (33x control in SC HDm, 41x control in SH HDm!!).
Reduced P excretion in all treatment groups (0.02x control in SC HDm and 0.009x control in SH HDm!!).

Urinary parameters

	Males					Females				
Dose-level (mg/kg/day) Test item	0	1000 (SC)	4500 (SC)	1000 (SH)	4500 (SH)	0	1000 (SC)	4500 (SC)	1000 (SH)	4500 (SH)
pH	7.2	**8.3****	7.5	**7.9***	**8.0****	6.3	6.5	6.3	6.2	6.6
Na/Crea	15.9	**11.6****	**13.1***	**8.7****	15.1	14.4	**10.5***	11.9	**9.5****	13.3
K/Crea	15.7	13.8	15.2	14.4	13.7	21.8	**17.7****	**18.1***	**18.4***	**17.0****
Cl/Crea	13.4	**10.4***	**10.1****	**9.7****	**21.2****	12.6	**9.8***	9.9	11.4	**17.7**
Ca/Crea	0.11	**0.74***	**3.66****	0.57	**4.49****	0.31	**0.65****	**2.96****	0.52	**1.56****
Pho/Crea	5.35	**0.24****	**0.12****	0.98	**0.05****	9.25	**3.75****	**0.65****	**4.73***	**1.52****

SC: Sevelamer carbonate, SH: Sevelamer hydrochloride
Statistically significant from controls, *: $p<0.05$; **: $p<0.01$.

Gross pathology: No treatment-related changes were noted

Organ weights: No treatment-related effects on organ weights were noted

Histopathology: No treatment-related changes were noted

Study title: 4-week Toxicity Study by Oral Route (Capsules) in Beagle Dogs

Key study findings: Toxicology profile for sevelamer bicarbonate is similar to that of sevelamer hydrochloride.

Study no.: GT-153-TX-2 (24922 TSC)
Volume #4, and page #140:
Conducting laboratory and location:

[redacted]

Date of study initiation: 23 January 2003
GLP compliance: yes
QA report: yes (x) no ( )
Drug, lot #, and % purity:
Sevelamer carbonate: X2365915
Sevelamer hydrochloride: 2336955

Methods

Doses:
Control (methylcellulose): 1000 mg/kg/day
Sevelamer carbonate (SC): 200 or 1000 mg/kg/day

Sevelamer hydrochloride (SH): 200 or 1000 mg/kg/day
Species/strain: Canine/Beagle
Number/sex/group or time point (main study):
40 (20m, 20f) 4m and 4f per group (one control, 4 treatment)
Route, formulation, volume, and infusion rate:
Oral, capsule, 2 or 7 capsules, once per day
Satellite groups used for toxicokinetics or recovery: na
Age: approximately 7 weeks old
Weight: males: 7.7 kg (range: 5.8-8.4 kg), females: 7.1 kg (range: 6.3-7.8 kg)
Unique study design or methodology (if any): none

Observation and Times: (this information can be provided in a separate section OR evaluation times can be described for each parameter in the results section).
Clinical signs: At least twice per day
Body weights: Daily
Food consumption: Daily
Ophthalmoscopy: Prior to treatment period and at end of treatment period
EKG: Prior to treatment period, and 2 hours after final dose
Hematology: Prior to treatment period and at end of treatment period
Blood biochemistry: Prior to treatment period and at end of treatment period
Urinalysis: Weekly (selected parameters). Prior to treatment period and at end of treatment period for all parameters.
Gross pathology/Organ weights/Histopathology: At end of treatment period

Results:

Mortality:
No unscheduled deaths

Clinical signs:
Emaciated appearance in some animals: 1/4 LDf SC, 1/4 HDm SC, 1/4 LDm SH.

Body weights:
Changes in mean body weight were similar in the treated and control animal groups. However, it was noted that the control animals did not gain weight during the study period to the extent that would normally be expected.

Food consumption: No treatment-related changes were noted

Ophthalmoscopy: No treatment-related changes were noted

EKG: No treatment-related changes were noted

Hematology: No treatment-related changes were noted

Clinical Chemistry:

Vitamin D: Treated females had a 25-30% drop from pre-treatment levels (control animals had a 10% drop over the same period).
Vitamin E: HD SH-treated animals had 35%(m) and 45%(f) drops from pre-treatment levels. HDf SC-treated animals had a 40% drop from pre-treatment levels. Controls had 5%(m) and 15% drops from baseline over the same period.

Vitamins A, D and E levels

		Males					Females				
Dose-level (mg/kg/day)	Time	0	200	1000	200	1000	0	200	1000	200	1000
Test Item			SC	SC	SH	SH		SC	SC	SH	SH
Vitamin A (µg/ml)	predose	2.08	2.11	1.92	1.82	2.24	1.77	1.66	1.62	1.33	1.76
	week 4	2.22	2.32	1.98	2.04	2.41	1.56	1.75	1.60	1.45	1.62
Vitamin D (pg/ml)	predose	196.6	259.9	225.9	193.0	248.6	200.4	244.7	219.3	217.9	186.5
	week 4	145.1	217.9	149.5	165.8	184.0	180.8	187.6	166.1	173.4	122.4
Vitamin E (µg/ml)	predose	7.21	8.87	8.99	7.89	8.80	6.99	8.68	10.99	9.46	10.44
	week 4	6.94	7.54	8.08	7.31	5.73	6.10	8.71	6.53	7.27	5.59

SC: Sevelamer Carbonate, SH: Sevelamer Hydrochloride

Urinalysis:

Increased Ca^{2+} with HD SH (2.5x baseline at week 4).

Increased Cl^- with HD SH (1.7(f)-2.3(m)x baseline at week 4).

* *Calcium/creatinin ratio:*

Dose-level (mg/kg/day)	0	200 SC	1000 SC	200 SH	1000 SH
Week					
Males					
Predose	0.25	0.31	0.36	0.28	0.30
1	0.14	0.22	0.19	0.27	0.77*
2	0.24	0.40	0.26	0.31	0.92**
3	0.22	0.40	0.38	0.43	0.80**
4	0.29	0.37	0.38	0.48	0.74
Females					
Predose	0.44	0.54	0.39	0.29	0.27
1	0.33	0.23	0.39	0.29	0.38
2	0.39	0.45	0.50	0.63	0.67
3	0.31	0.28	0.39	0.37	0.36
4	0.33	0.28	0.30	0.50	0.67

Statistically significant from controls, *: $p<0.05$, **: $p<0.01$.

* *Chloride/creatinin ratio:*

Dose-level (mg/kg/day)	0	200 SC	1000 SC	200 SH	1000 SH
Week					
Males					
Predose	29.2	18.5	22.1	22.3	19.6
1	9.4	12.6	8.6	18.2	26.4*
2	16.7	16.9	10.0	20.5	34.8
3	16.7	16.3	14.0	20.9	27.1
4	28.0	25.1	26.5	45.0	44.6
Females					
Predose	29.7	27.5	20.6	18.5	30.6
1	10.8	12.9	14.0	16.2	22.7**
2	20.8	17.4	19.0	22.9	29.8
3	21.5	21.0	17.7	26.2	34.9*
4	25.2	32.3	24.4	28.2	51.4*

Statistically significant from controls, *: $p<0.05$, **: $p<0.01$.

Gross pathology: No treatment-related changes were noted

Organ weights:

Thymus: Smaller thymi were noted in males and females receiving either dose of SC. Effect of SC is dose-dependent in males, but not females. Thymi were larger in HD SH-treated animals and smaller in LD SH-treated animals.
Ovaries and Uterus: Larger in all treatment groups. Attributed to differences in sexual maturation on the basis of microscopic examination.

	Males					Females				
Group	1	2	3	4	5	1	2	3	4	5
Test item		SC		SH			SC		SH	
Dose-level (mg/kg/day)	0	200	1000	200	1000	0	200	1000	200	1000
Body weight	-	-1	-8	-8	-4	-	-3	-3	-0	-3
- *Thymus*										
. absolute	-	-14	-35	-22	+2	-	-21	-14	-3	+6
. relative	-	-13	-28	-19	+10	-	-21	-12	-1	+10
- *Ovaries*										
. absolute	-	-	-	-	-	-	+252	+107	+97	+76
. relative	-	-	-	-	-	-	+252*	+110	+102	+84
- *Uterus*										
. absolute	-	-	-	-	-	-	+375	+274	+266	+117
. relative	-	-	-	-	-	-	+373	+284	+279	+132

*: statistically significant ($p<0.05$)

Histopathology: No treatment-related changes were noted.

Other:

Histopathology inventory (optional)

Study	GT-153-TX-1	GT-153-TX-2
Species	Rat	Dog
Adrenals	*X	*X
Aorta	X	X
Bone Marrow smear		X
Bone (femur)	X	
Brain	*X	* X
Cecum	X	X
Cervix	X	X
Colon	X	X
Duodenum	X	X
Epididymis	*X	*
Esophagus	X	X

Eye	X	X
Fallopian tube	X	X
Gall bladder		X
Gross lesions	X	X
Harderian gland	X	
Heart	*X	* X
Ileum	X	X
Injection site		
Jejunum	X	X
Kidneys	*X	* X
Lachrymal gland		
Larynx	X	X
Liver	*X	* X
Lungs	X	* X
Lymph nodes, cervical		
Lymph nodes mandibular	X	X
Lymph nodes, mesenteric	X	X
Mammary Gland	X	X
Nasal cavity		
Optic nerves	X	X
Ovaries	*X	* X
Pancreas	X	X
Parathyroid	*X	*X
Peripheral nerve		
Pharynx		
Pituitary	X	* X
Prostate	*X	X
Rectum	X	X
Salivary gland	X	X
Sciatic nerve	X	X
Seminal vesicles	X	
Skeletal muscle	X	X
Skin	X	X
Spinal cord	X	X
Spleen	*X	* X
Sternum	X	X
Stomach	X	X
Testes	*X	* X
Thymus	*X	* X
Thyroid	*X	* X
Tongue	X	X
Trachea	X	X
Urinary bladder	X	X
Uterus	*X	* X
Vagina	X	X
Zymbal gland		

X, histopathology performed
*, organ weight obtained

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/s/

Xavier Joseph
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