

SPECIAL TOXICITY**1. Effect of PB-94 on urine volume and excretion of electrolytes in rats (I): Urine collected over 6 hours**

Study nr. TX95-317

Method

Male Slc:SD rats (n=8/group) received single doses of 0, 20, 200, 2000 mg/kg orally, by gavage, after overnight fast and forced urination. Controls received distilled water. Animals were given no food or water for 6h. Urine was collected for 6 h post dose, at 6h urination was forced. Blood samples and stomach removed 6h postdose.

Results

Urine parameters:

200 mk: Urine pH increased; K excretion increased to large extent, Na and Cl excretion increased to slight extent

2000 mk: Urine volume decreased; pH increased; osmotic pressure increased; Na markedly increased, Ca, IP excretion increased, K and Cl excretion unaffected

Urine osmolality: Increased in HD; when corrected for Na, K, Cl, Ca, P still elevated in HD (137-127-129-210), possibly due to increased concentrations of other urine components.

Gastric contents: Stomach empty in LD, MD. In HD, retention of PB-94 and water in stomach (0.64 ml, n=8).

Urinary electrolyte excretion (mEq/6h/100g)

dose (mk)	volume (ml/6h/100g)	pH	osmolality (mOsm)	Na	K	Cl	Ca	IP
control	3.5	6.2	240	35	79	41	40	2
20	3.6	6.3	224	34	72	35	43	1.9
200	3.5	6.5	254	50	130*	47	44	2.1
2000	2.6↓	6.5	385	84↑*	63	50	59↑	2.6↑

*significant effect

Serum electrolyte concentrations (mEq/l Na, K, Cl, mg/dl Ca, IP)

dose (mk)	Cl	Ca	IP
control	102.5	10.1	7.6
20	103.3	10.1	7.6
200	104.2	10.1	7.4
2000	106.5↑*	10.1	7.4

*significant effect

Conclusions

Urine appears concentrated, and Na/K is elevated at high Renagel dose

Increased serum Cl might be due to high Cl content (20%w/w) of test article

Urinary Ca level and excretion were increased; cause unclear.

Increased P excretion cause unclear.

PB-94 effects on urine volume and electrolytes may be related to retention of water in GI tract (animals were not given water after dosing)

2. *Effect of PB-94 on urine volume and excretion of electrolytes in rats (II): Urine collected over 24 hours*

Study nr. TX96-306

Method

Male Slc:SD rats (n=8/group) received single doses of: **Renagel 0, 20, 200, 2000 mg/kg, cholestyramine (2000 mg/kg), NH₄Cl (484 mg/kg)**, orally, by gavage, after overnight fast and forced urination. Vehicle was distilled water. Urine collected for 24 h post dose. Methods are unclear whether animals were given food and water during those 24h. Blood samples after 24h. Cholestyramine and NH₄Cl doses contained equal amounts of Cl as 2000 mg/kg dose of Renagel.

Results

200 mk: Na, K, Cl excretion slightly increased, P excretion slightly decreased

2000 mk; Urinary osmotic pressure increased; Na, K, Cl, Ca excretion increased. IP excretion decreased.

Cholestyramine: Urine osmolarity increase, pH decrease, Na, K, Cl, Ca excretion increase. P decrease

NH₄Cl: Urine volume increase, osmolarity increase, pH decrease, Na, K, Cl, Ca increase. P no effect

Urinary electrolyte excretion (mEq/24h/100g)

dose (mk)	volume (ml/24h/100g)	pH	osmolarity (mOsm)	Na	K	Cl	Ca	P
control	4.7	6.2	699	252	300	239	88	9.2
20	4.3	6.2	697	246	261	227	81	8.5
200	4.3	6.2	731	270	284	282	84	7.9
2000	5.1	6.3	873*	464*	412*	917*	149*	6.9*
cholestyramine	4.3	5.7*	897*	312*	350*	700*	128*	7.5*
NH ₄ Cl	6.3↑*	5.7*	829*	463*	417*	1160*	315*	9.6

Serum electrolyte concentrations (mEq/l Na, K, Cl, mg/dl Ca, IP)

dose (mk)	Cl	Ca	IP
control	104.3	10	8.3
20	103.9	10	8.4
200	104.2	10	8.5
2000	104.6	10	8.6
cholestyramine	103.6	9.9↓*	8.2
NH ₄ Cl	105.1	10	8.6

APPEARS THIS WAY
ON ORIGINAL

Conclusions

No volume reduction as in previous study

Increased Cl excretion is likely to be due to Cl absorption from test article. Data from cholestyramine and NH₄Cl confirm this.

Increase in Na and K excretion probably related to Cl excretion, in case of all three test articles.

Increased Ca excretion by Renagel and cholestyramine may be related to Cl loading:
 NH₄Cl same effect.

Decreased P excretion may be due to P binding by Renagel or cholestyramine. However,
 opposite result seen in previous 6h study.

Serum electrolyte levels unchanged: renal function compensates

All urine electrolyte (Na, K, Ca, Cl) changes except P decrease by Renagel also seen with
 NH₄Cl; thus, Cl content of administered compound may explain these effects

3. EFFECT OF PB-94 ON URINE VOLUME AND EXCRETION OF ELECTROLYTES IN RATS (III): INVESTIGATION OF THE MECHANISM OF ACTION

Study nr. TX96-315

Purpose

In previous studies increased urinary Cl and Ca secretion in rats was seen upon dosing
 with Renagel. To test the hypothesis that the increased Cl secretion was due to the Cl
 contained in the polymer dosing formulation (ca. 19% w/w), the Cl in PB-94 was
 replaced with phosphate or carbonate, and administered to rats. Also, serum PTH and
 ALP, and urine cAMP, creatinine and deoxy pyridinoline, and creatinine clearance were
 measured to evaluate effects on bone metabolism.

Methods

Preparations of PB-94:

PB-94 19.1%Cl

PB-P1 1.7%Cl

PB-P2 0.2%Cl

PB-C 0.1%Cl

Male Slc:SD rats (n=8/group) received single doses of **0, 2000 mg/kg PB-x**, orally, by
 gavage (40ml/kg) after overnight fast and forced urination. Vehicle was distilled water.
 Animals were not given food or water for 24h. Urine collected for 24 h post dose. Blood
 samples after 24h.

Results

When suspended in artificial intestinal fluid (50 ml) PB-94 (2.5g) released 20-35 mEq/l
 Cl. When suspended in artificial gastric fluid (50 ml) PB-P1 and PB-P2 (2.5g) released
 17 and 45 mg/dl IP.

Urine analysis:

No effects on volume

No significant effects of any PB-x on serum Na, K, Cl, Ca, IP concentrations

No effects of PB-x on urinary cAMP, deoxy, creatinine

No effects of PB-x on serum creatinine, ALP, PTH, creatinine clearance

Urinary electrolyte excretion (mEq/24h/100g)

dose (mk)	pH	osmolality (mOsm)	Na	K	Cl	Ca	P
control	6.1	856	240	277	182	98	9.5
PB-94	6.0	1013*	448*	373*	870*	142*	6.8

PB-P1	5.85*	857	301	313	203	87	15.1
PB-P2	5.59*	838	339*	337*	191	81	21.2*
PB-C	6.51*	837	272	319	132	76	8.1

*significantly different

Conclusions

Urinary Cl excretion is related to Cl content of PB formulation. Changes in urinary Na and K excretion generally parallel those in urinary anion (Cl or IP) excretion. Mechanism of increased Ca excretion, also seen with eg NH_4Cl , is unclear. Ca metabolism parameters do not suggest bone effect.

4. EFFECT OF PB-94 ON GASTRIC EMPTYING IN RATS

Study nr. TX95-326

Slc:SD rats were treated orally, with **20, 200, 2000 mg/kg**, after 24h fast. Gastric emptying was studied with acetaminophen method

Serum acetaminophen concentration was reduced in HD, although not significantly.

Conclusion

Renagel can inhibit gastric emptying in rats

5. EFFECT OF PB-94 ON INTESTINAL TRANSPORT IN MICE

Study nr. TX95-320

Slc:ddY mice (8/group) were fasted o/n, treated orally with **0 (water) 20, 200, 2000 mg/kg** PB-94, then administered 50% BaSO_4 , orally, 30 minutes after PB-94. Animals were killed 30 min after BaSO_4 administration, and distance traveled by BaSO_4 in small intestine was determined.

Results

BaSO_4 transport rate in HD was significantly increased.

Conclusion

Intestinal transport can be stimulated by PB-94 in mice.

6. STUDY ON GASTROINTESTINAL TRANSPORT OF PB-94 IN MICE

Study nr. TX95-312

Slc:ddY mice (8/group) were fasted o/n, then treated orally with **2000 mg/kg** PB-94 (50 mg/ml), containing 0.5% charcoal powder as a marker. Stomach removed at 1, 2, 4, 6h post dosing.

Results

PB-94 remained in stomach up til 6h after administration, and was not transported into small intestine. Stomach dry weight did not change over 6h, wet weight decreased.

Conclusion

In fasting mice, PB-94 remains in stomach. Gastric emptying of H_2O does occur.

7. EFFECTS OF PB-94, ADMINISTERED IN DIET FOR TWO WEEKS, ON BLOOD COAGULATION IN RATS

Study nr. TX95-316

Methods

Slc:SD rats (8sex/group) were treated with 0%, 0%, 10% (9.4 g/kg/day) PB-94, orally, in the diet, for 2 weeks. Control groups received either basal diet, or diet with 10% (m9.1-f9.3 g/kg/day) cellulose. Animals were fasted o/n after 15 days of dosing, and tests were performed on Day 16: APTT (reflects intrinsic clotting pathway), PT (extrinsic pathway), RBC/WBC/platelet count, platelet aggregation, and euglobulin clot lysis time (fibrinolytic system).

Results

Necropsy (Day 16) -

1 treated m had hemorrhage in testes and epididymis

Hematology -

RBC decreased in animal with hemorrhages

WBC not affected

Coagulation -

APTT, PT (Table): Largest APTT was seen in animal with hemorrhages. APTT was correlated to PT (r^2 0.87f, 0.97m)

	males		females	
	APTT	PT	APTT	PT
control	20.6	13.5	18.7	13.4
cellulose	20.9	12.9	17.5	13.9
PB-94	27.2*	13.7	22.7*	14.4

*significantly different from cellulose

Collagen-induced platelet aggregation was inhibited in PB-94 group, particularly in hemorrhaging animal, but not significantly due to large variability. ADP-induced aggregation was not affected by PB-94.

Euglobulin clot lysis time was unaffected by PB-94.

Conclusions

Hemorrhages in testes and epididymis occurred within 2 weeks of dose administration, similarly to results in previous multiple dose toxicity studies.

Both intrinsic and extrinsic pathway of coagulation factors was inhibited by substance.

Hemorrhage appears to be related to increased APTT and PT.

Coagulation effect is possibly due to reduced absorption of vitamin K, which affects the biosynthesis of factors IX (i), II (e), II and V (i and e)

Effect on platelet aggregation is unexplained, and could be result or (partial) cause of hemorrhaging.

8. A 9-WEEK RANGE-FINDING TOXICITY STUDY OF RENAGEL ADMINISTERED BY A VITAMIN-SUPPLEMENTED DIETARY ADMIX TO MICE

Study nr. GT-01-TX-18.

GLP statement included, but no QA. July-September 1996. Lot nrs. RS9501HRE and 14248NI00.

Purpose

Determine toxicity of Renagel when administered by a vitamin A, D, E, and K - supplemented dietary admix to mice

Methods

Albino [CrI:CD-1(ICR)BR] mice (10 males/dose group), 3 weeks old, weighing 30-37g, were treated with 3g/kg/day of Renagel, via diet admix for 9 weeks. Food and water was available ad libitum. 5/group were sacrificed after ca. 4 weeks, to obtain serum vitamin levels. 5/group were sacrificed after 9 weeks, blood taken and gross necropsy performed. No histopathology done.

Dose levels of Renagel and Vitamins A,D,E, K added to standard diet

	Group	N (males)	Dose levels				
			Renagel (mg/kg/day)	VitA (IU/kg diet)	VitD (IU/kg diet)	VitE (IU/kg diet)	VitK (ppm)
<i>Standard Certified Rodent Diet</i>	<i>All</i>			17600	2200 (Vit D3)	66.1	0.4
Control groups	1	8	0	0	0	0	0
Renagel groups	2	8	0	2500	750	320	10
	3	8	3	0	0	0	0
	4	8	3	2500	375	160	10
	5	8	3	2500	750	320	10

Results

Mortality - None

Clinical signs - None

BW - No effects

FC - No effect

Ophthalmology - No data

Serum vitamin levels -

VitD no effects (all groups ca. 30 ng/ml, wks 4 and9)

VitA lower at wk9 than wk4; no diet or drug effects

VitE lower at wk9 than at wk4; Vits 2 supplementation increases level in controls at both wk4 and wk9; At wk4, Vit E level is reduced by Renagel, and Vits 1,2 supplements reverse the level clearly. At wk 9, both effects of Renagel and of vitamin supplementation are not clear.

VitA, VitE

Group	VitA		VitE	
	Wk4	Wk9	Wk4	Wk9
1 control	0.32	0.20	2.1	1.4
2 control+Vits2	0.30	0.19	2.4	1.9
3 Renagel	0.27	0.16	1.3	1.5
4 Renagel+Vits1	0.31	0.25	2.1	1.2
5 Renagel+Vits2	0.27	0.14	2.7	1.7

Organ weights - No treatment-related effects
 Gross pathology - No findings
 Histopathology - Not performed

Conclusions

1. Vitamin supplementation in controls appears to increase only serum vitamin E level. The data on standard diet vitamin contents submitted by fax (9/1/98), entered in the Table above (Methods) indicate that there was sufficient supplementation of Vitamin E and K, but not of Vitamin A and D. This explains lack of effect on Vitamin A levels.
2. Renagel reduces serum vitamin E levels; this effect appears partially reversed by vitamin supplement.
3. The decrease of Vitamin A and E levels in week 9 as compared to week 4 is explained by Sponsor as a result of difference in standard curves (Fax 9/30/98). This explanation is unacceptable, and the serum vitamin values may be inaccurate.
4. Only serum levels of vitamins were measured; tissue levels may be changed differently than serum levels.
5. No other drug effects seen: dose level chosen was too low.

9. A 9-WEEK RANGE-FINDING TOXICITY STUDY OF RENAGEL ADMINISTERED BY A VITAMIN-SUPPLEMENTED DIETARY ADMIX TO RATS

Study nr. GT-01-TX-18. _____ . GLP statement included, but no QA. July-September 1996. Lot nrs. RS9501HRE and 14248NI00.

Purpose

Determine toxicity of Renagel when administered by a vitamin A, D, E, and K - supplemented dietary admix to rats

Methods

Albino (Sprague Dawley Crl:CD) rats, 8 males/dose group, 13 weeks old, weighing 350-380g, were treated with 3g/kg/day of Renagel, via diet admix for 9 weeks. Food and water was available ad libitum. Animals were sacrificed after 9 weeks, blood taken and gross necropsy performed. No histopathology done.

Dose levels of Renagel and Vitamins A,D,E, K

	Group	N (males)	Dose levels				
			Renagel (mg/kg/day)	VitA (IU/kg diet)	VitD (IU/kg diet) (Vit D3)	VitE (IU/kg diet)	VitK (ppm)
<i>Standard Certified Rodent Diet</i>	<i>All</i>			17600	2200	66.1	0.4
Control groups	1	10	0	0	0	0	0
Renagel groups	2	10	0	2500	750	320	10
	3	10	3	0	0	0	0
	4	10	3	2500	375	160	10

RENAGEL NDA 20,926

	5	10	3	2500	750	320	10
--	---	----	---	------	-----	-----	----

Results

Mortality - None

Clinical signs -

Group	Signs
control	none
control+Vits2	none
Renagel	1m: urine discolored, red (on several days), nose red discharge, chromodacryorrhea, pallor, dyspnea, eyes and legs black stain 1m: chromodacryorrhea
Renagel+Vits1	1m: chromodacryorrhea, chromorhinorrhea
Renagel+Vits2	1m: chromorhinorrhea

BW - Mean BW values Wk9: 571 - 565 - 529 - 536 - 528

Slight reduction in Renagel groups. not reversed by vitamin supplement

FC - No effects

Ophthalmology - No data

Serum vitamin levels -

Vitamin E level increased by vitamin supplementation.

Vitamin D, E levels decreased by Renagel.

Vitamin D, E levels partially restored by supplementation of Renagel diet with vitamins, at wk4 and wk9.

Vitamin A level not affected by Vitamin supplement, or by Renagel.

VitA, VitE, VitD

	VitA		VitE		VitD	
	Wk4	Wk9	Wk4	Wk9	Wk4	Wk9
control	1.1	0.98	3.3	3.9	17	21
control+Vits2	1.1	0.97	4.7	5.4	19	25
Renagel	0.93	0.92	2.3	1.7	10.5	15
Renagel+Vits1	1.03	0.97	4.0	2.9	15	23
Renagel+Vits2	0.96	1.1	4.9	3.7	12	27

Coagulation values -

	PT (sec)	APTT (sec)
	Wk9	Wk9
control	14.9	13.5
control+Vits2	14.8	12.0
Renagel	16.5*	15.0**
Renagel+Vits1	14.9	10.9
Renagel+Vits2	15.1	11.9

*Value increased due to 1 animal with high PT 27.5 sec

**Value increased due to 2 animals with high APTT>20sec

Organ weights -

Liver weight slightly decreased, not reversed by vitamin supplement

Epididymes slightly increased, reversed by vitamin supplement

Organ weights	Liver		Epididymes	
	abs	rel	abs	rel
control	15.6	2.73	1.51	0.27
control+Vits2	15.4	2.72	1.43	0.26
Renagel	13.3↓	2.52↓	1.62↑	0.31↑
Renagel+Vits1	14.2	2.64	1.47	0.28
Renagel+Vits2	13.2	2.5	1.45	0.28

Gross pathology - No findings

Histopathology - Not performed

Conclusions

1. Chromodacryorrhea, chromorhinorrhea, red urine indicates blood coagulation problem in Renagel groups with/out vitamin supplement
2. Small drug-related body weight reduction, not affected by vitamin supplementation.
3. Vitamin supplementation in controls appears to increase serum vitamin E level.
4. Renagel reduces vitamin E and D levels; this effect appears to be reversed by vitamin supplement. Data on standard diet vitamin content (see Table, Methods) in accordance with findings on Vitamin E. Supplementation of Vitamin D was inadequate, and cause of reversal of serum Vitamin D level may be unrelated to Vitamin D supplementation itself.
5. Only serum levels of vitamins A,D,E were measured; tissue levels may be changed differently than serum levels.
6. Coagulation parameters indicate impaired blood clotting in a few animals; effect reversed by vitamin supplementation.
7. Liver weight reduced in all Renagel groups with/out vitamins. Epididymal weight increase reversed by vitamin supplement.
8. Dose level chosen was fairly low, since effects were small or only seen in a few animals.

10. 28-DAY ORAL TOXICITY IN HARLAN SPRAGUE DAWLEY (HSD) RATS AND CHARLES RIVER SPRAGUE-DAWLEY (CD) RATS

Study nr. GT-01-TX-21

See NONCLINICAL TOXICOLOGY (Study Nr.4)

LABELING

Draft labeling was submitted with the NDA (Vol. 1.1, p.0043).

APPENDIX II contains:

1. A strikethrough-underline version of the label with revisions as originally drafted by Pharmacology/Toxicology (1st round).
2. Comments to the label after the first response from Sponsor (2nd round).
3. A revised draft labeling. A labeling meeting was held with the Sponsor on Friday October 2, 1998, and comments of the Division to the Sponsors first response were discussed. The resulting changes have been incorporated in the revised draft labeling. Draft was faxed by Sponsor to Division on 10/5/98.

**APPEARS THIS WAY
ON ORIGINAL**

SUMMARY AND EVALUATION

NONCLINICAL PHARMACOLOGY

Pharmacology

Renagel appears to bind phosphate. Renagel increases fecal P excretion and dose-dependently decreases urinary P excretion in normal rats. This suggests that Renagel can interfere with P absorption.

Safety pharmacology

Renagel appeared to have no effect on behavioral, neurological or autonomic profiles, or on spontaneous motor activity or body temperature in male mice. Also, it had no anesthetic potential, anticonvulsive or analgesic actions in male mice. The highest dose tested in these studies was 2000 mg/kg, which on basis of body weight is approximately 20 times the highest average dose used in the clinical trials.

A 2000 mg/kg dose (20 x human intended dose, body weight basis) Renagel did not affect respiratory or cardiovascular systems in anaesthetized male beagle dogs.

An unexplained contractile response to Renagel was observed in guinea pig ileum and rat gastric fundus preparations.

Drug interaction

The potential of Renagel to alter pharmacokinetics of a number of drugs was evaluated in the dog. The oral dose applied was 100 mg/kg, ie, approximately 1x the average human dose required in the trials. The relevance of these data is limited because:

1. the difference in gastrointestinal physiology between species
2. clinical drug-drug interaction studies have not been performed

Pharmacology/toxicology studies indicate that Renagel can interfere with the absorption of fat and fat-soluble vitamins, at least partially through its capacity to bind bile acids. It therefore seems likely that Renagel will interfere with absorption of other apolar molecules or substances it can bind. This issue will be addressed by the Biopharmaceutical and Medical Reviewers.

NONCLINICAL PHARMACOKINETICS

In vitro data indicate that Renagel is degraded very slowly, both chemically as well as biologically, in the gastrointestinal tract.

Excretion and blood and tissue level studies with radioactive compound show that the level of Renagel in blood and tissues is extremely low. However, the level is higher than the level of soluble components in the administered dose formulation, when expressed as percent of dose. In other words, some tissue distribution of intact or degraded polymer in addition to soluble oligomer occurs. In rats the distribution is mainly to GI tissues, liver and brown fat, in dogs to GI tissues, liver, blood, skin, fat and muscle. Nevertheless, in both species the major part of an administered dose appears to remain in the GI tract to be excreted with the feces, and not enter the systemic circulation.

Excretion and tissue distribution studies

	PK Study nr.	Collection time	Fecal excretion	Urinary excretion	Biliary excretion	Expired air excretion
Rat	2	0-96h	94.7%	<0.05%	nd	nd
	4A	0-72h	96-103%	nd	0.003%	0.08%
	4B	0-72h	87-108%	nd	0.03%	0.01%
	6	0-48h	101-112%	0.04%	0.004%	0.05%
	8	0-72h	98-105%	0.05%	nd	nd
Dog	5	0-72h	94%	0.03%	nd	nd
	7	0-48h	98%	0.07%	nd	nd

Tissue distribution

	Study nr.	Soluble components	Sampling time (h postdose)	Blood level (% of dose)	Total tissue level (% of dose)	Number of tissues
Rat	2	0.01%	4 or 8h	0.04% (Cmax)	0.02-0.03% (Cmax)	3
	3	0.04%	6h	BDL	>0.06-0.09%*	31
	8	no data	72h	0.01%	0.05%	10
Dog	5	0.12%	6h	0.06%	0.35-0.37%	18
			72h	BDL	BDL	18
	7	no data	48h	BDL	0.47%	11

*GI tissues and brown fat not included: nd = no data

TOXICOLOGY

Single and multiple dose oral toxicology studies were done in rats and dogs. Rat studies were done in Hsd or CD rats for 1, 3, 6 months with a highest dose of 6 g/kg/day in the 6-month study and 10 g/kg/day in all other studies. All rat studies were done by dietary administration, and in all rat studies but one the control animals received cellulose at the high dose level. Study results are summarized in the following tables:

Rat studies

Number	Sponsor's number	Duration	Doses	SD breed	NOAEL	Mortality	Mortality due to	Clinical signs
1	TX-1	28 days	0-1-4.5-10	Hsd	1 g/kg/day	1/10 HDm	Hemorrhage	Paleness, discharge ear, thin, swollen testes
2	TX95-125	1 month (+ recovery)	0-0.3-1-3-10	Slc	1 g/kg/day	None	-	Hemophthalmia, large black feces
3	TX-9	28 days	0-1-4.5-10	Crl	1 g/kg/day	8/10 HDm	Hemorrhages	Paleness, red discharges
4	TX-21	28 days	10	Hsd, Crl (males only)	<10 g/kg/day	None	-	Paleness, decreased activity, red staining
5	TX-16	90 days	0-1-2-4.5-10	Hsd	1 g/kg/day	3/15 HDm	Hemorrhage	Chromodacryorrhea
6	TX-6	26 weeks	0-0.6-3-6	Hsd	<0.6 g/kg/day	1/20 HDm	Hemorrhage	None

*water consumption increased too

RENAGEL NDA 20,926

Rat studies: Toxicities

Parameters	Effect (study numbers effect was observed in)
Body weight	Decreased in m or in m,f in all studies
Food consumption	Increased in m,f (2,4,5), or decreased (3)
Hematology	RBC, Hb, Hct decrease m>f (1,2,3,4,5) MCV decrease m (1,3) MCH and MCHC increase m,f (2,5) WBC, platelets, neutrophils, or reticulocytes increase m,f (1,2,3,4,5) PT and aPTT increase m,f (2,3,4)
Urinalysis	Volume increase (2) PH decrease (2) Na, K excretion increase (2) Ca excretion increase (2) Cl excretion increase (2,3) P excretion decrease (2) Osmolarity increase (2)
Clinical Chemistry	Vitamin E decrease m,f (1,2,3,4,5) Vitamin D decrease m,f (1,3,5,6) Vitamin A decrease m,f (3) Serum Cl increase m (1,2), or decrease m,f (3,5,6) P increase m,f (1,5,6), or decrease m,f (2) BUN increase m,f (1,3,5,6) ALP increase m,f (1,2,3,4) Albumin and/or protein decrease m, f (1,2,3,6), or increase in albumin m (2) Ca increase (2,5), or decrease m (3) Fe increase m,f (2), or decrease m,f (1,3,6) Cu increase m,f (1,6) ALT, AST increase m,f (1,3,5,6) Glucose increase m (1,3) Triglycerides increase m (1,3), or decrease m (2) Cholesterol increase or decrease m,f (3,6) Phospholipid increase f (2)
Relative organ weights	Testes and/or epididymes increase (1,3,5) Adrenal increase m (1,2,3,4) Brain increase m (1,2,3,4,5) Liver decrease m (2,4), increase f (5) Kidney increase m,f (5,6) Ovary increase (3)
Gross Pathology	Multiple organ hemorrhages in animals that died (1,3,5,6) Epididymes and testes hemorrhages and swelling (1,3,4) Lymph nodes red (1,3) Thymus red (1,3) Eye, prostate, jejunum, ileum red foci (2)
Histopathology	Hemorrhages in various organs (1,2,3,5) Testis and epididymes: hemorrhage, degeneration, edema, inflammation, necrosis (1,3,4) Pancreas inflammation, acinar cell degeneration (1,6) Spinal cord hemorrhage (5) Lung inflammation, hemorrhage (4) Lung mineralization (5) Kidney mineralization (5) Thymus hemorrhage, necrosis (1,3,4,5,6) Liver/spleen increased hematopoiesis (1,2) Liver hepatitis, necrosis (4,5,6) Congestion and erosion in small intestine (2) Stomach edema submucosa f>m (all doses) (5,6) Rectum edema submucosa (m,f) (5) Ileum/colon lymphoid hyperplasia (5) Uterus dilated lumen (5) Femur, sternbrae physcal dysplasia (decreased osteoid disposition in primary spongiosa, and widened cartilage) (3) Stomach calcification upon recovery (2)

RENAGEL NDA 20,926

Beagle dog studies were done with a highest dose of 2 g/kg/day for 1, 3, 12 months. All dog studies were done with dosing by capsule, and in 3/5 studies controls received cellulose (2/5 with recovery no cellulose control). Studies are summarized in the tables below.

Dog studies

Number	Sponsor's number	Duration	Doses	Dosing	NOAEL	Mortality
1	TX-3 (females only)	28 days	0-0.12-0.4-1.2	In feed	0.4 g/kg/day	None
2	TX-2	28 days	0-0.2-1-2	Capsule	0.2 g/kg/day	None
3	CH95147	28 days (+ recovery)	0-0.2-0.6-2	Capsule	0.2 g.kg.day (based on BW effect)	None
4	TX-7	13 weeks	0-0.2-1-2	Capsule	0.2 g/kg/day (based on clin chem)	1 MDm (hemorrhage in heart/GI)
5	TX-10	52 weeks (+ recovery)	0-0.2-0.6-2	Capsule	0.2 g/kg/day based on hematomol and clin chem)	None

Dog studies: Toxicities

Parameter	Effect (study numbers effect was observed in)
Clinical signs	Yellow or orange colored stool (2,3), colored or coated feces (5)
Body weight	Decrease in m>f (2,3), or no change (1,4,5)
Food consumption	No effects
Water consumption	Increase in m,f (3,5)
EKG	No effects
Hematology	RBC, Hb, Hct decrease (1,4,5) MCH decrease (3) MCV increase and MCHC decrease (5) Platelet count decrease (2) PT increase (3)
Urinalysis	Volume increase (5) Cl and Ca excretion increase (3,4,5) Na, K excretion decrease (??) (4) P excretion increase (5) Urobilinogen decrease m,f (2)
Clinical Chemistry	Vitamin D decrease m,f (2,4,5) Vitamin E decrease (2,3,4,5) Cl increase m,f (1,2,3,4,5) Ca decrease f (1) P increase m,f (4) Cholesterol decrease m,f (2,3,4,5) Triglycerides decrease m,f (2,4,5) Fe decrease m,f (2), increase m (5) ALT increase m (2) ALP increase (bone/liver) m,f (6) Phospholipid decrease m (3), f (5) Folic acid decrease m,f (6)
Relative organ weights	Spleen decrease m (3) Liver increase m (5) Kidney increase m (5)
Gross Pathology	Colon dark area f (2) Hemorrhage in heart, intestine (animal died) (4) Lung dark are m,f (4) Stomach thickened (2,5)

BEST POSSIBLE COPY

Histopathology	Bone marrow increased hematopoiesis f (2) Esophagus erosion m (2) Lymph node hemorrhage m (2) Liver gallbladder hemorrhage f (3) Thymus lymphoid atrophy m (2), necrosis (4) Lung pneumonia f (4) Spleen capsular fibrosis (1,5) Testes hemorrhage MD (5) Tonsil hemorrhage MD (5) Kidney decreased tubular pigment deposition w lipofuscin m,f (5)
----------------	--

In the rat toxicity studies, the main drug-related findings were dose-dependent decreases in the serum levels of the fat soluble vitamins D and E, and A. The hemorrhages observed in all studies were probably related to a concomitant decrease in serum levels of Vitamin K. The decrease in prothrombin time measured in most studies, and the decrease in vitamin K levels measured in one study support this hypothesis. The anemia and the other blood cell and platelet changes may be the result of the hemorrhages, or may be due to the vitamin E deficit leading to impaired cell membrane integrity. The submucosal edema in stomach and rectum seen in the 3 and 6 month studies appears to be a drug-induced toxicity.

The NOAEL in the rat was 1 g/kg/day in 1 month studies, <1 g/kg/day in the 3 month study, and <0.6 g/kg/day in 6 month. These values are approximately 6-10 times the intended clinical dose (9-12 capsules/day, or 3.6-4.8 g/day or 72-96 mg/kg/day) on the basis of body weight comparison. Since this compound is virtually not absorbed and confined to the gastrointestinal compartment, comparison on the basis of body weight is appropriate for this compound.

The LOAEL was 3-4.5 g/kg/day in the 1-month studies, 1 g/kg/day in the 3-month study, and 0.6 g/kg/day in the 6-month study. The toxicities that occur at the lowest LOAEL value of 0.6 g/kg/day (6x clinical dose, body weight basis) in the 6-month study are a decrease in serum levels of vitamin E and Fe, and stomach submucosal edema. In the 3-month study, thymus hemorrhage occurred at the LOAEL of 0.6 g/kg/day (6 x clinical dose, body weight basis). Serum vitamin K level was reduced at 10 g/kg/day, as measured in one study.

In the dog toxicity studies, similar findings as in the rat were obtained. There were a decrease in body weight, decreases in the serum levels of vitamin D and E, anemia, changes in Cl, Ca and P serum levels and excretion, elevation of PT, decreases in cholesterol and triglyceride, increase in ALP, and hemorrhages in several organs. The change in body weight is either the result of an effectively decreased food intake or an inhibitory effect of vitamin levels on metabolism. The other changes can be explained by interference with fat and vitamin D, E and K absorption from the GI tract. The increased Cl level and excretion is probably the result of the high Cl content of the Renagel drug substance. Increased Ca excretion has also been observed in the rat with Cl loading. However, the increase in serum P and excretion is unexplained. Esophagus erosion and stomach thickening are other possibly relevant drug toxicities.

The NOAEL in the dog was 0.2 g/kg/day. The LOAEL was 0.6 g/kg/day. These values are 2 and 6 times the intended clinical dose on body weight basis. The toxicities that

occurred at the LOAEL of 0.6 g/kg/day (6x clinical dose, body weight basis) were anemia, vitamin E, vitamin K and folic acid decrease, and hemorrhaging in the 12-month study. At 1 g/kg/day mortality due to hemorrhaging occurred in 1/4 males in the 3-month study. At 2 g/kg/day vitamin D levels were decreased.

Animal toxicities observed are relevant for the clinical situation, and adverse events related to impaired vitamin D, E and K absorption and blood coagulation, and GI tract adverse events should not be considered unexpected.

REPROTOXICITY

A Segment I study in rats and two Segment II studies in rats and rabbits were performed. At doses up to 4.5 g/kg/day Renagel had no effect on male or female fertility in the rat. At doses of 1.5 and 4.5 g/kg/day, Renagel causes reduced or irregular ossification of fetal bones in the rat. This finding may be related to a decreased absorption of the fat soluble Vitamin D, as indicated by general toxicity studies in this species.

At a dose of 1g/kg/day, Renagel caused an increase in the number of early resorptions in the rabbit.

A study of perinatal and postnatal development (Segment III study) was not carried out, and the Segment I study that was carried out did not include parturition and lactation. Thus, there was no evaluation of parturition and lactation and no evaluation of F1 offspring in any of the reprotoxicity studies. A Segment III study was not required for filing of the NDA.

From the results of general toxicity and reprotoxicity studies, it can be predicted that problems with parturition and lactation are to be expected at doses that are sufficiently high to interfere with vitamin absorption. This issue needs to be addressed in the label, which should state which reprotoxicity studies were done and which were not ("PRECAUTIONS": "Pregnancy", "Labor and Delivery", "Nursing mothers"). The positive findings in the Segment I and II studies and the lack of a Segment III study warrant the designation "Pregnancy Category C".

This Reviewer feels that a Phase IV commitment for a Segment III study with Renagel is not required.

GENOTOXICITY

Renagel was non-mutagenic in bacterial reverse mutation assays with Salmonella typhimurium and E.Coli, when tested as saline extract of test compound, or as suspension of compound in DMSO.

An in vitro mammalian cytogenetics test showed that Renagel induced structural chromosome aberrations at the extended 44h sampling time at doses between 1250 and 5000 ug/ml. In the summary of Nonclinical Pharmacology and Toxicology (Vol. 1.10, section 5.5, p.139), the Sponsor states that "the weakly positive effects of Renagel are thought to be due to Renagel's ability to absorb the culture medium and not the direct action of the test article." However, this hypothesis is contradicted by the fact that the test was negative in the absence of metabolic activation and at the other sampling times. This Reviewer concludes that the positive result indicates the potential for clastogenicity of

Renagel. Additional in vitro testing would have to be performed to obtain more information on this issue.

In the in vivo micronucleus assay Renagel did not produce micronuclei in the bone marrow of the mouse, at intraperitoneal doses up to 2300 mg/kg/day. However, Renagel is unlikely to be absorbed into the systemic circulation via this dose administration route, and probably does not reach the target bone marrow tissue. Therefore, unless it can be substantiated by data showing sufficient marrow exposure, the in vivo test and its results are not considered valid.

CARCINOGENICITY

In the End of Phase II Meeting with the Sponsor on February 26, 1996, the firm stated that because of 25% per year mortality rate for an end stage renal failure indication no carcinogenicity studies should be required, and the Division concurred. However, carcinogenicity studies with Renagel are currently in progress, but have not been completed. The Sponsor is carrying out the studies in the context of Japanese and European registration. Studies were started in October, 1996. Results need to be requested.

SPECIAL TOXICITY

Three studies were performed to evaluate the effect of single doses of Renagel on urine volume and electrolyte excretion in the male rat. The results were compared to those with cholestyramine and NH_4Cl . The increase in serum Cl and in Na, K, Cl and Ca excretion seen in toxicity studies with Renagel may be explained by the high load of Cl in the test article. The mechanism of increased Ca excretion is unclear.

The results on the effects of Renagel on gastrointestinal transport were unclear and confusing, probably due to differences in dose administration in relation to water and food intake.

The blood coagulation study in rats showed that Renagel at doses of approximately 9 g/kg/day inhibits blood clotting through inhibition of both the intrinsic and extrinsic pathway. This effect is most likely the result of a reduced absorption of the lipid soluble vitamin K from the GI tract. The reduced absorption can be due to either binding of vitamin K to Renagel or indirectly due to decreased fat absorption through binding of bile acids to Renagel. There was also an unexplained inhibitory effect of Renagel on platelet aggregation.

In two 9-week toxicity studies in rats and mice, the combined effect of dietary vitamin supplementation and Renagel (dose 3 g/kg/day) on serum vitamin levels and gross pathology was investigated. The supplements given were adequate for vitamin E and K, but not for vitamin A and D.

In the mouse, Renagel reduced the serum vitamin E level, which was reversed by dietary vitamin supplementation. There was no drug-related toxicity in the mouse.

In the rat, Renagel caused a slight incidence of bleeding from eyes, nose, and urine. Vitamin D and E levels were reduced, and blood coagulation was inhibited. Vitamin

supplementation partially reversed serum vitamin D and E levels, and reversed blood coagulation impairment, but did not completely prevent chromodacryorrhea or chromorhinorrhea. Renagel also reduced body and liver weight, which effects were not reversed by vitamin supplement. Epididymal weight increase by Renagel was prevented by vitamin supplementation.

LABELING

Labeling was incomplete. The suggested changes have been documented and are attached in APPENDIX II. Revised label as of 10/5/98 has also been attached.

RECOMMENDATION

Approval (AP)

Recommendation is based on the following:

1. Nonclinical pharmacokinetic studies have indicated that Renagel polymer is confined mainly to the gastrointestinal compartment and is excreted for the major part in the feces.
2. Main preclinical toxicities observed in rats and dogs consisted of reduced serum levels of vitamins D, E and K, probably due to the binding of bile acids by Renagel, and the consequent impairment of lipid and lipid-soluble vitamin absorption. The vitamin deficiency related toxicities included anemia, hemorrhaging in various organs and death (at doses ranging from 6-100 times the intended human dose, on body weight basis). However, in the clinical trials, RBC, serum vitamin levels and prothrombin time were not affected, at up to 44 weeks of treatment. Therefore, the preclinical toxicities are unlikely to occur at the intended human dose.
3. The reproductive toxicities observed in rats and rabbits were also most likely due to impaired vitamin absorption during gestation. These findings need to be mentioned in the package insert, and warrant the label designation Pregnancy Category C.
4. The in vitro genotoxicity tests were valid, the in vivo micronucleus test was not. The results of the in vitro CHO test raises the possibility of clastogenicity. Although there is minimal systemic exposure to the drug when orally administered, the gastrointestinal tract lining cells will be exposed to relatively high levels of Renagel, and could be affected if compound is clastogenic. Carcinogenicity studies with Renagel are ongoing and may clarify this issue. Pending the results of the carcinogenicity studies, the mutagenesis findings can be addressed in the label.

^A
/S/

Gemma Kuijpers, Ph.D.

/S/

10/13/98

APPENDIX I
List of Studies

Table 5.4: Nonclinical Efficacy Studies

SECTION NO.	STUDY TITLE	SPECIES	TREATMENT DURATION	DOSE	SUBMITTED TO IND	GLP
5.2.3.1	<i>in vitro</i> Binding of RenaStat to Phosphate. (Study No GI-01-EF-1)	--	--	--	No	No
5.2.3.2	Studies to Evaluate the Effects of RenaStat (GI16-026A) on Fecal Phosphorus Excretion in Normal Rats. (Study No GI-01-EF-3)	Rat	5 days	11.7% (w/w)	46,601-000 Oct. 27, 1994	No
5.2.3.3	A Study to Evaluate the Effects of RenaStat (GI16-026A) and Calcium Carbonate on Fecal Phosphorus Excretion in Normal Rats. (Study No GI-01-EF-4)	Rat	5 days	11.7% (w/w)	46,601-000 Oct. 27, 1994	No
5.2.3.4	A Pilot Study to Evaluate the Test Article in a Model of Renal Secondary Hyperparathyroidism and Hyperphosphatemia in Rats. (Study No GI-01-EF-2)	Rat	49 days	0-10% (w/w)	46,601-000 Oct. 27, 1994	No
5.2.3.5	The Effects of RenaStat (GI16-026A) on the Mass Balance of Phosphorus Excretion in Normal Rats Fed a High Phosphorus Diet. (Study No GI-01-EF-5)	Rat	7 days	8 and 12% (w/w)	46,601-000 Oct. 27, 1994	No

SECTION NO.	STUDY TITLE	SPECIES	TREATMENT DURATION	DOSE	SUBMITTED TO IND	GLP
5.2.3.6	The Effect of RenaGel on Urinary Phosphorus Excretion in Normal Rats. (Study No GI-01-EF-6, GI-01-EF-7, GI-01-EF-8)	Rat	4 days	0.5-9.0% (w/w)	No	No
5.2.4.1	The Effects of RenaGel on Bile Acid Mass Excretion in Fat Fed Hamsters (Study No GI-01-EF-9)	Hamster	2 days	0.2-0.6% (w/w)	No	No

BEST POSSIBLE COPY

**APPEARS THIS WAY
ON ORIGINAL**

BEST POSSIBLE COPY

Table 5.6: Nonclinical Safety Pharmacology

SECTION NO.	STUDY TITLE	SPECIES	TREATMENT DURATION	DOSE	SUBMITTED TO IND	GLP
5.2.5.1	Effects of PB-94 on General Activity and Behavior in Mice (Study No TX95-314)	Mice	1 day	0.02, 0.2, 2.0 g/kg	No	Yes
5.2.5.2	Effect of PB-94 on Central Nervous System in Mice(I): Effects on Spontaneous motor Activity and Body Temperature. (Study No TX95-319)	Mice	1 day	0.02, 0.2, 2.0 g/kg	No	Yes
5.2.5.3	Effect of PB-94 on Central Nervous System in Mice(II): Effect on Hexobarbital Induced Sleeping Time, Electroshock-Induced Convulsions, and Acetic Acid Writhing. (Study No TX95-315)	Mice	1 day	0.02, 0.2, 2.0 g/kg	No	Yes
5.2.5.4	Effect of PB-94 on Respiratory and Cardiovascular System in Anesthetized Dogs. (Study No TX95-315)	Dog	1 day	2.0 g/kg	No	Yes
5.2.5.5	Effect of PB-94 on Isolated Smooth Muscle (Study No TX95-321)	---	1 day	0.05, 0.5, 5.0 mg/ml	No	Yes

APPEARS THIS WAY
ON ORIGINAL

Table 5.10: Nonclinical Pharmacokinetic Studies

SECTION NO.	STUDY TITLE	SPECIES	TREATMENT DURATION	DOSE (g/kg)	SUBMITTED TO IND	GLP
5.3.2.1	Degradation of PB-94 in Gastrointestinal Contents (Study No AD96-006)	Rat	2 days	N/A	No	No
5.3.2.2	Disposition and Excretion of Cross-linked Polymer Hydrogel (CPII) [¹⁴ C]G116-026A in Rats (Study No GI-01-PK-1)	Rat	1 day	0.10	46.601-000 Oct. 27, 1994	Yes
5.3.2.3	Pharmacokinetics Studies on PB-94 (II): Absorption and Distribution in Male Rats after a Single Oral Administration of [¹⁴ C]PB-94. (Study No DPC/AE-2326-2G)	Rat	1 day	0.25	No	Yes
5.3.2.4	Pharmacokinetics Studies on PB-94 (III): Excretion in Male Rats after a Single Oral Administration of [¹⁴ C]PB-94. (Study No DPC/AE-2326-3G)	Rat	1 day	0.25	No	Yes
5.3.2.5	Pharmacokinetics Studies of PB-94 (V): Excretion in Male Rats after a Single Oral Administration of [³ H]PB-94. (Study No DPC/AE-2326-5G)	Rat	1 day	0.25	No	Yes
5.3.2.6	Pharmacokinetics Studies of PB-94 (IV): Absorption, Distribution, and Excretion in Male Dogs after a Single Oral Administration of [³ H]PB-94. (Study No DPC/AE-2326-4G)	Dog	1 day	0.25	No	Yes

SECTION NO.	STUDY TITLE	SPECIES	TREATMENT DURATION	DOSE (g/kg)	SUBMITTED TO IND	GLP
5.3.2.7	Pharmacokinetics Studies of PB-94 (I): Absorption, Distribution, and Excretion in Rats and Dogs. (Study No AE-2275)	Rat Dog	1 day	0.25	No	Yes
5.3.2.8	Open Balance Study of ¹⁴ C-Polyallylamine (Renagel) Following Oral Administration to Dogs. (Study No GI-01-PK-2)	Dog	1 day	0.20	46.601-000 Oct. 27, 1994	Yes
5.3.2.9	Absorption, Distribution and Excretion of Radioactivity in Sprague-Dawley Rats Following Oral Administration via Gavage of a Single Dose of [³ H]-Labeled Renagel (G116-026A) With and Without Unlabeled Renagel Pretreatment via Feed for One Month. (Study No GI-01-PK-4)	Rat	28 days 1 day	6.0 0.250	46.601-000 May 13, 1996	Yes

BEST POSSIBLE COPY

APPEARS THIS WAY
ON ORIGINAL

Table 5.17: Nonclinical Toxicology Studies: Single Dose Studies

SECTION NO.	STUDY TITLE	SPECIES	TREATMENT DURATION	DOSES (G/KG)	SUBMITTED TO IND	GLP
5.4.2.1	Single Oral Dose Toxicity Study of PH-94 in Rats. (Study No TX95-117).	Rat	1 day	0, 1.0, 2.0	No	Yes
5.4.2.2	Single Oral Dose Toxicity Study of PH-94 in Dogs. (Study No TX95-118)	Dog	1 day	2.0, 4.0	No	Yes

BEST POSSIBLE COPY

**APPEARS THIS WAY
ON ORIGINAL**

BEST POSSIBLE COPY

Table 5.18: Repeated Dose Toxicity Studies

SECTION NO.	STUDY TITLE	SPECIES	TREATMENT DURATION	DOSES (g/kg)	SUBMITTED TO IND	GLP
5.4.3.1	A 28-Day Oral Toxicity Study of RenaStat (GT16-026A) in Rats. (Study No GI-01-TX-1)	Rat	28 days	1.0, 4.5, 10.0 10.0 cellulose	46,601-000 Oct. 27, 1994	Yes
5.4.3.2	1-Month Repeated Dose Toxicity Study of PB-94 in Rats (Study No TX95-125)	Rat	1 month	0, 0.3, 1.0, 3.0, 10.0 10.0 cellulose	No	Yes
5.4.3.3	4-Week Dietary Toxicity Study with RenaGel (GT16-026A) in Rats. (Study No GI-01-TX-9)	Rat	28 days	0, 1.0, 4.5, 10.0	No	Yes
5.4.3.4	Twenty-Eight Day Safety and Toxicity Study of the Test Articles Administered in the Feed to Dogs (Study No GI-01-TX-3)	Dog	28 days	0, 0.12, 0.4, 1.2	46,601-000 Oct. 27, 1994	No
5.4.3.5	A 28-Day Oral (Capsule) Toxicity Study of RenaStat (GT16-026A) in the Beagle Dog (Study No GI-01-TX-2)	Dog	28 days	0.2, 1.0, 2.0 4 capsules cellulose	46,601-000 Oct. 27, 1994	Yes
5.4.3.6	1-Month Repeated Dose Toxicity Study of PB-94 in Dogs. (Study No CI95147)	Dog	1 month	0, 0.6, 2.0	No	Yes

SECTION NO.	STUDY TITLE	SPECIES	TREATMENT DURATION	DOSES (g/kg)	SUBMITTED TO IND	GLP
5.4.3.7	A Twelve Week Oral Toxicity Range-Finding Study of RenaGel (GT16-026A) in Rats (Study No GI-01-TX-5)	Rat	12 weeks	0, 0.6, 2.0, 6.0	No	No
5.4.3.8	A 90 Day Oral (Diet) Toxicity Study of RenaGel (GT16-026A) in Rats. (Study No GI-01-TX-16)	Rat	90 days	1.0, 2.0, 4.5, 10.0 10.0 cellulose	No	Yes
5.4.3.9	A 13 and 26-Week Oral (Diet) Toxicity Study of RenaGel (GT16-026A) in Rats. (Study No GI-01-TX-6)	Rat	13 weeks 26 weeks	0.6, 3.0, 6.0 6.0 cellulose	46,601-000 May. 13, 1996	Yes
5.4.3.10	A 13-Week Oral (Capsule) Toxicity Study of RenaGel (GT16-026A) in the Beagle Dog. (Study No GI-01-TX-7)	Dog	13 weeks	0.2, 1.0, 2.0 4 capsules cellulose	46,601-000 May. 13, 1996	Yes
5.4.3.11	A 12-Month Oral (Capsule) Toxicity Study of RenaGel (GT16-026A) in the Beagle Dog. (Study No GI-01-TX-10)	Dog	1 Year	0, 0.2, 0.60, 2.0	No	Yes

Table 5.36: Reproductive Toxicity Studies

SECTION NO.	STUDY TITLE	TREATMENT DURATION	DOSES (g/kg)	SUBMITTED TO IND	GLP
5.4.5.1	Oral Fertility Study of Renagel (GT16-026A) in Rat. (Study No. GT-01-TX-13)	*	0, 0.5, 1.5, 4.5 4.5 Cellulose	No	Yes
5.4.5.2	A Dietary Teratology Study of Renagel (GT16-026A) in Rats. (Study No. GT-01-TX-14)	Days 7-17 of gestation	0, 0.5, 1.5, 4.5 4.5 Cellulose	No	Yes
5.4.5.3	An Oral Range-Finding Teratology Study of Renagel (GT16-026A) in the Rabbit. (Study No. GT-01-TX-8)	Days 7-19 of gestation	0, 0.15, 0.5, 1.5	No	Yes
5.4.5.4	An Oral Teratology Study of Renagel (GT16-026A) in the Rabbit. (Study No. GT-01-TX-15)	Days 6-18 of gestation	0, 0.1, 0.5, 1.0	No	Yes

*Males were dosed for 4 weeks prior to mating and throughout the mating period. Females were dosed for 2 weeks prior to mating, throughout the mating period and from Day 0 through Day 7 of gestation.

BEST POSSIBLE COPY

**APPEARS THIS WAY
ON ORIGINAL**

Table 5.44: Genotoxicity Studies

SECTION NO	STUDY TITLE	SPECIES	TREATMENT DURATION	DOSE	SUBMITTED TO IND	GLP
5.4.6.1	<i>Salmonella typhimurium</i> Reverse Mutation Assay (Study No G1-01- (X-4)	---	---	5 mg/ml	46-011-000 Oct. 27, 1994	Yes
5.4.6.2	Reverse Mutation Test on PH-94 in Bacteria. (Study No TX95-217)	---	---	5 mg/ml	No	Yes
5.4.6.3	<i>In vitro</i> Mammalian Cytogenetic Test. (Study No GT-01-TX-11)	---	---	5 mg/ml	No	Yes
5.4.6.4	Micronucleus Cytogenetic Assay in Mice. (Study No GT-01-TX-12)	Mice	2 days	5.0 g/kg	No	Yes

BEST POSSIBLE COPY

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

Table 5.48: Special Toxicity Studies

SECTION NO.	STUDY TITLE	SPECIES	TREATMENT DURATION	DOSES (G/KG)	SUBMITTED TO IND	GLP
5.4.7.1	Effect of PB-94 on Urine Volume and Excretion of Electrolytes in Rats (I): Urine collected Over 6 Hours. (Study No. TX95-317)	Rat	1 day	0.02, 0.20, 2.0	No	Yes
5.4.7.2	Effect of PB-94 on Urine Volume and Excretion of Electrolytes in Rats (II): Urine collected Over 24 Hours. (Study No. TX96-306)	Rat	1 day	0.02, 0.20, 2.0	No	Yes
5.4.7.3	Effects of PB-94 on Urine Volume and Electrolyte Excretion in Rats (III): Investigation of the Mechanism of Action. (Study No. TX96-315)	Rats	1 day	2.0	No	Yes
5.4.7.4	Effect of PB-94 on Gastric Emptying in Rats. (Study No. TX95-326)	Rat	1 day	0.02, 0.20, 2.0	No	Yes
5.4.7.5	Effect of PB-94 on Intestinal Transport in Mice (Study No. TX95-320)	Mouse	1 day	0.02, 0.20, 2.0	No	Yes
5.4.7.6	Study on Gastrointestinal Transport of PB-94 in Mice. (Study No. TX95-312)	Mouse	1 day	2.0	No	Yes
5.4.7.7	Effects of PB-94, Administered in Diet for Two weeks, on Blood Coagulation in Rats. (Study No. TX95-316)	Rat	14 days	10% (w/w) diet	No	Yes

SECTION NO.	STUDY TITLE	SPECIES	TREATMENT DURATION	DOSES (G/KG)	SUBMITTED TO IND	GLP
5.4.7.8	28-Day Oral Toxicity Study in Harlan Sprague Dawley (Hsd) Rats and Charles River Sprague-Dawley (CD) Rats. (Study No. GT-01-TX-21)	Rat	28 days	0, 10.0	No	Yes
5.4.7.9	A 9-Week Range-Finding Toxicity Study of RenaGel Administered by a Vitamin-Supplemented Dietary Admix to Mice. (Study No. GT-01-TX-18)	Mouse	9 weeks	0, 3.0	No	No
5.4.7.10	A 9-Week Range-Finding Toxicity Study of RenaGel Administered by a Vitamin-Supplemented Dietary Admix to Rats. (Study No. GT-01-TX-17)	Rat	9 weeks	0, 3.0	No	No

APPEARS THIS WAY
ON ORIGINAL

APPENDIX II
Label

10

Page(s) Redacted

DRAFTING LABELING