Mean body weights (g) in males

	Control	5 mg/kg	15 mg/kg	30 mg/kg	60 mg/kg
Initial	222.2	224.4	222.3	224.2	221.8
13 weeks	523.7	529.3	530.6	524.0	524.2
26 weeks	593.2	596.5	601.3	593.2	590.0
52 weeks	663.7	671.8	673.2	653.6	638.3
78 weeks	657.3	681.3	690.9	641.5	635.8
Terminal	556.3	503.2 (91%)	512.6 (92%)	593.7 (107%)	506.6 (91%)

Mean body weights (g) in females

	Control	5 mg/kg	15 mg/kg	30 mg/kg	60 mg/kg	120 mg/kg
Initial	188	185	187	185	189	186
13 weeks	306	304	303	299	293	291
26 weeks	339	335	342	333	323	322
52 weeks	391	395	395	375	370	359
78 weeks	442	444	442	422	394	370
Terminal	425	416 (98%)	391 (92%)	426 (100%)	398 (94%)	391 (92%)

Control = mean of 2 control groups combined,
The numbers in parenthesis are % of control

The growth curves were depicted in Figure D2 on page 111 in volume 1.52. This figure is attached below.

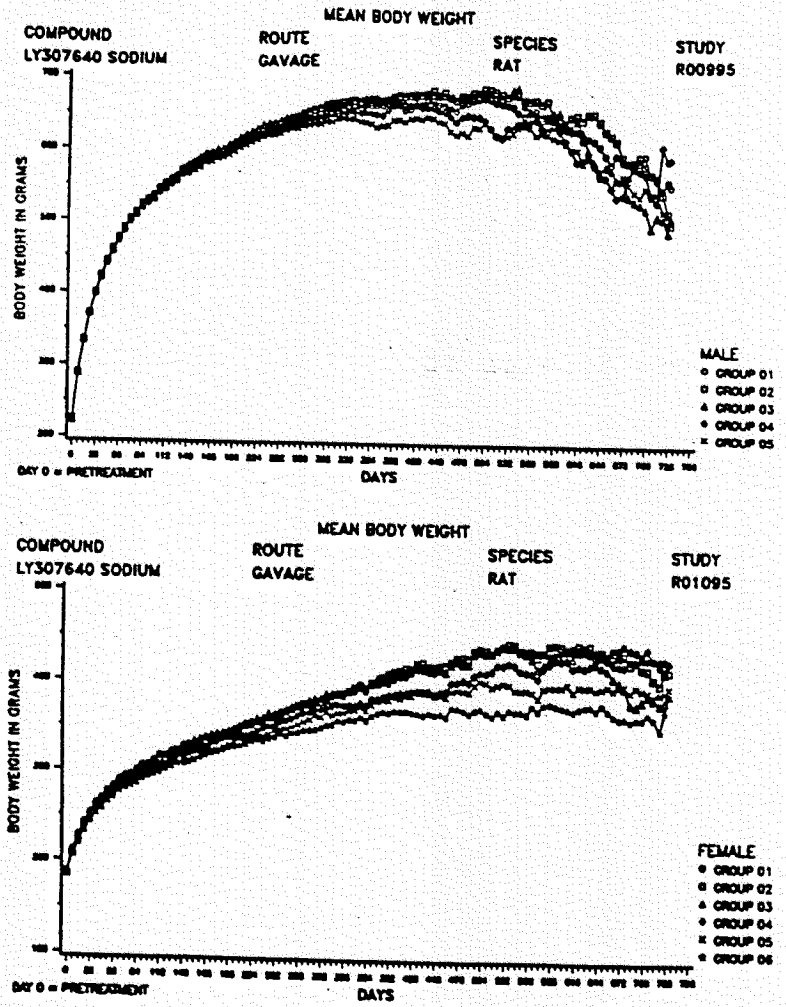

Figure D2 Mean Body Weight.

4. Food Consumption: Average food consumption in the control group was 23-25.4 (males) or 16.4-17.9 (females) g/rat/day. The food consumption was slightly but significantly increased (up to 4%) in males treated at 30 and 60 mg/kg. The food consumption was slightly but significantly decreased (up to 5%) in females treated at 60 and 120 mg/kg.

5. Ophthalmology Examination: There were no treatment related changes.

6. Hematology: There were no treatment related changes

7. Clinical Chemistry: Gastrin level was significantly increased in a dose dependent manner and this increase was transient and seen in all treatment groups. This information is summarized in the following table.

Mean gastrin level (pg/ml) in males

	Control	5 mg/kg	15 mg/kg	30 mg/kg	60 mg/kg
Initial	50.9	61.6	50.6	96.8	51.2
13 weeks	60.9	68.8	84.0	94.0	119.8
26 weeks	92.1	128.4	421.4	450.4	597.2
52 weeks	77.0	165.0	430.0	444.0	588.0
81 weeks	71.0	309.0	411.0	686.0	762.0
Terminal	80.3	74.7	101.1	124.0	103.0

Mean gastrin level (pg/ml) in females

	Control	5 mg/kg	15 mg/kg	30 mg/kg	60 mg/kg	120 mg/kg
Initial	42.7	43.6	51.2	54.0	45.4	54.2
13 weeks	48	125	299	533	683	574
26 weeks	66	205	336	453	476	488
52 weeks	57	156	378	447	517	643
78 weeks	88	172	407	434	609	685
Terminal	72.6	94.8	72.0	80.4	99.8	101.2

The other treatment related changes were summarized in a table on page 213 in volume 1.52 and this table is attached below.

Percentage Change in CHOL, TRIG, GLOB, ALB, and TP in Female Rats Given 10, 30, 60, or 120 mg/kg of LY307640 Sodium Orally for Approximately 2 Years

Dose (mg/kg)	CHOL	TRIG	GLOB	ALB	TP
15	45*	NC	20*	-6NS	NC
30	31*	NC	10*	-5NS	NC
60	63*	86*	17*	-6*	NC
120	63*	84*	13*	-9*	NC

*p<0.05, two-tailed trend T on ranked data.
NS = Not statistically significant.
NC = No change or no important change.

Percentage changes of CHOL (cholesterol), TRIG (Triglycerides), and GLOB (globulin) were increases as compared to the control.
ALB = albumin, TP = total protein.

8. Gross Pathology: The incidence of thickening of the stomach wall was increased in the treated animals (2, 10, 11 and 11 in males treated at 5, 15, 30 and 60 mg/kg and 0, 3, 6, 11 and 11 in females treated at 5, 15, 30, 60 and 120 mg/kg) as compared with control (4, 2 in control1 and control2 males and 0, 1 in control1 and control2 females). The incidence of the renal cysts were increased in the treated animals (9, 2, 11 and 16 in males treated at 5, 15, 30 and 60 mg/kg and 4, 2, 2, 7 and 9 in females treated at 5, 15, 30, 60 and 120 mg/kg) as compared with control (2, 5 in control1 and control2 males and 0, 2 in control1 and control2 females).

9. Histopathology:

Non-neoplastic Changes: The significant and dose-related histopathological changes were observed in the stomach and kidney and this information was summarized in tables on pages 6 and 7 in volume 1.53. These tables are attached below.

Treatment-Related Changes in the Gastric Glandular Mucosa (Males)

Group:	00	01	02	03	04	05
Dose (mg/kg/day)	0	0	5	15	30	60
No. Tissues Examined/Group	70	70	70	70	70	70
Glandular Hyperplasia	8	7	17	29	41	46
ECL Cell Hyperplasia	0	0	0	0	1	2
Eosinophilic Granules/Chief Cells	11	10	17	30	51	51
Increased Secretory Deposits	1	0	1	15	42	62

Treatment-Related Gastric Changes Observed Microscopically (Females)

Group:	00	01	02	03	04	05	06
Dose (mg/kg/day)	0	0	5	15	30	60	120
No. Tissues Examined/Group	60	60	60	60	60	60	60
Carcinoid Neoplasms (Benign)	0	0	1	3	5	4	5
Carcinoid Neoplasms (Malignant)	0	0	0	0	1	1	2
Carcinoid Neoplasms (Combined)	0	0	1	3	6	5	7
Neuroendocrine Cell Hyperplasia	0	0	1	3	12	14	23
Glandular Hyperplasia	3	3	10	30	40	47	51
Eosinophilic Granules/Chief Cells	6	3	15	40	55	57	56
Increased Secretory Deposits	0	0	2	18	37	46	52

Treatment-Related Microscopic Changes in Kidney Tissues (Males)

Group:	00	01	02	03	04	05
Dose (mg/kg/day)	0	0	5	15	30	60
No. Tissues Examined/Group	70	70	70	70	70	70
Nephropathy	65	63	67	69	67	70
Average Severity[a]	3.41	3.17	3.60	3.93	3.90	3.96
Tubular Cysts	29	33	35	41	52	46
Glomerulosclerosis	33	35	37	47	52	50

[a] Average severity based upon grading scale where: normal = 0, minimal = 1, slight = 2, moderate = 3, severe = 4, and marked = 5.

Treatment-Related Renal Changes Observed Microscopically (Females)

Group:	00	01	02	03	04	05	06
Dose (mg/kg/day)	0	0	5	15	30	60	120
No. Tissues Examined/Group	60	60	60	60	60	60	60
Nephropathy (CPN)	36	35	39	48	46	50	52
Average Severity[a]	1.43	1.47	1.40	1.88	1.70	2.07	3.20
Tubular Cysts	2	3	3	4	1	5	15
Glomerulosclerosis	8	7	6	8	10	13	30

[a] Average severity based upon grading scale where: normal = 0, minimal = 1, slight = 2, moderate = 3, severe = 4, marked = 5.

Glandular hyperplasia was characterized by a diffuse increase in thickness of the glandular mucosa with minimal-to-moderate elongation of glandular units. Chronic progressive nephropathy was characterized by dilated, protein filled tubular, thickened glomerular and tubular basement membranes, institial fibrosis and infiltrates of mixed inflammatory cells, glomerulosclerosis and tubular cysts. Other changes were the increased incidence of diffuse fibrous osteodystrophy in both males and females and bilateral minimal follicular epithelial hypertrophy of the thyroid in females (0, 0, 0, 1, 0, 4 and 15 in the 0, 0, 5, 15, 30, 60 and 120 mg/kg groups, respectively). The incidence of diffuse fibrous osteodystrophy is summarized in the following table.

Incidence of diffuse fibrous osteodystrophy

	Con1	Con2	5 mg/kg	15 mg/kg	30 mg/kg	60 mg/kg	120 mg/kg
	Males						
Total numbers examined	70	70	70	70	70	70	
Minimal	6	4	3	8	9	5	--
Slight	4	3	7	10	13	10	--
Moderate	4	3	5	7	5	8	--
Severe	2	3	0	2	3	3	--
Total	16	13	15	27	30	26	--
	Females						
Total numbers examined	60	60	60	60	60	60	60
Minimal	0	0	0	1	0	0	3
Slight	1	2	1	0	2	2	2
Moderate	1	0	0	0	1	3	8
Severe	0	0	0	1	0	1	3
Total	2	2	1	2	3	6	16

Neoplastic Changes: There were no treatment related changes in the tumor incidences in males. However, in females, the treatment produced malignant and benign carcinoid tumors in the stomach. The incidence of malignant carcinoid tumors in the stomach in females was 0, 0, 0, 0, 1, 1 and 2 in the control1, control2, 5, 15, 30, 60 and 120 mg/kg groups, respectively. The incidence of benign carcinoid tumors in the stomach in females was 0, 0, 1, 3, 5, 4 and 5 in the control1, control2, 5, 15, 30, 60 and 120 mg/kg groups, respectively. The combined tumor incidence was 1, 3, 6, 5 and 7 in 5, 15, 30, 60 and 120 mg/kg groups, respectively. Most of these tumors were detected at termination except that in the animals found dead (one each female treated at 60 or 120 mg/kg/day) the tumors were found during week 100 or week 102 or in the animal sacrificed in the moribund condition (one female treated at 60 mg/kg/day) the tumor was found during week 92. The combined benign and malignant carcinoid tumors in the stomach were found to have positive linear trends using data from pooled control, 5, 15, 30, 60 and 120 mg/kg/day dose groups ($p<0.001$). Significant positivity is retained even after deleting 120 mg/kg/day group; 60 and 120 mg/kg/day groups; and 30, 60 and 120 mg/kg/day groups from comparisons. There was no significant heterogeneity found between the two control groups.

The incidence of non-neoplastic and neoplastic histopathological findings extracted from sponsor's tables H11 and H12 on pages 134-269 in volume 1.53 and pages 1-226 in volume 1.54 (non-neoplastic data) and tables H24-H31 on pages 295-310 in volume 1.54 (neoplastic data) is attached in Appendix III.

10. Drug Plasma Levels: Plasma levels of the parent compound and two metabolites (thioether and desmethyl thioether) were determined at 0.5 and 24 hours after dosing. These levels were below quantitation limit (22 ng/ml) at 24 hours after dosing. The mean plasma levels measured at 0.5 hours after dosing are summarized in the following table.

Mean plasma level (ng/ml)

	Males				Female				
	T1	T2	T3	T4	T1	T2	T3	T4	T5
Week	Parent Compound				Parent compound				
13	BQL	34	46	83	BQL	65	30	110	119
26	BQL	68	113	173	BQL	BQL	65	177	250
53	BQL	BQL	1667	2754	BQL	BQL	600	102	140
78	BQL	BQL	74	5291	53	1122	136	7294	25507
	Thioether				Thioether				
13	48	94	170	242	80	211	455	992	1482
26	86	61	184	326	72	195	385	1353	1456
53	35	53	164	551	87	219	445	617	1125
78	39	46	124	344	100	218	292	737	1474

	Desmethyl thioether				Desmethyl thioether				
13	BQL	34	50	67	27	38	57	129	166
26	BQL	BQL	54	93	24	35	63	182	205
53	BQL	BQL	BQL	73	BQL	24	45	58	106
78	BQL	BQL	32	58	32	34	44	100	143

BQL = Below quantitation limit

In general, the plasma concentrations (parent and metabolites) were increased with the doses and there was apparent accumulation of the parent drug over time.

In summary, in the 2-year oral carcinogenicity study in rats, rats (70 males/group or 60 females/group) were treated with rabeprazole by oral gavage at 0, 0, 5, 15, 30 and 60 mg/kg/day (males) or 0, 0, 5, 15, 30, 60 and 120 mg/kg/day (females) for 2 years. The dose selection was based on findings from the 3 month oral (gavage) toxicity study in rats (R31193, R31293 and R01994). In this study, MTD was identified at 25 mg/kg/day for males and 60 mg/kg/day for females. Both Division and CAC recommended sponsor to use doses of 7.5, 15 and 30 mg/kg/day in males and 15, 30 and 60 mg/kg/day in females. However, sponsor instead chose the doses of 5, 15, 30 and 60 mg/kg/day in males and 5, 15, 30, 60 and 120 mg/kg/day in females in the 2-year carcinogenicity study. In the current study, the high dose tested (60 mg/kg in males and 120 mg/kg in females) exceeded MTD since there were significantly increased mortality and histopathological changes in the stomach and kidney. Slightly lower (91-92%) in the body weight in the high dose group as compared to control was noted in both males and females. A significant increase in the mean gastrin level was seen in all treatment groups. There were no treatment related changes in the tumor incidence in males but in females malignant and benign carcinoid tumors in the stomach were detected in treatment groups (not in the control group). The incidence of the carcinoid tumors (malignant and benign) in the stomach in females was 0, 0, 1, 3, 6, 5 and 7 in the control1, control2, 5, 15, 30, 60 and 120 mg/kg groups, respectively. The combined benign and malignant carcinoid tumors in the stomach were found to have positive linear trends using data from pooled control, 5, 15, 30, 60 and 120 mg/kg/day dose groups ($p<0.001$). Significant positivity is retained even after deleting 120 mg/kg/day group; 60 and 120 mg/kg/day groups; and 30, 60 and 120 mg/kg/day groups from comparisons. There was no significant heterogeneity found between the two control groups.

REPRODUCTIVE TOXICITY:

Segment I. Fertility and General Reproductive Performance Study in Rats
(Study # 1079)

Testing Laboratories: [redacted]

Study Started: November 13, 1989

Study Completed: July 16, 1991

GLP Requirements: A statement of compliance with GLP regulation was included.

Animals: Male (about 7 week old, 200-235 g) and female (10 weeks old, 212-256 g) Sprague Dawley (Crj:CD SD) rats.

Drug Batch No.: 89010911 and 89120401

Methods: In this study, the dose selection was based on preliminary 4-week i.v. subacute toxicity study in rats in which doses of 1, 5, 25 and 50 mg/kg/day were used. Highest dose produced reduction of spontanious movement, decreased body weight gain and atrophy of the thymus. Hyperplasia of the gastric wall, increased liver weight, atrophy of the thymus and hypertrophy of thyroid follicular epithelia were observed at 25 mg/kg/day. In view of these findings the highest dose selected for the present study was 30 mg/kg/day.

In the main study, groups of 24 male and 24 female rats were given E3810 (dissolved in physiological saline at 0.1%, 0.6% or 3.0%) intravenously 0 (Saline), 1, 6 and 30 mg/kg/day. The volume of administration was fixed at 1 ml/kg. The male rats were treated from 63 days prior to mating and throughout the mating phase until they were sacrificed (total 67 days). Female rats were treated for 14 days prior to mating and throughout the mating phase. Additionally pregnant females which were used for C. sections were given the drug for 8 more days after mating whereas dams which were allowed to deliver naturally were given the drug till 20 days after postpartum. The volume of administration was fixed at 1 ml/kg. Parents were observed daily for mortality and toxic signs. Body weights and food consumptions were recorded weekly. The mating performance and fertility of both sexes were evaluated. Twelve pregnant rats were sacrificed on day 20 of gestation, and was examined for the number of corpora lutea, the number of implants, the number of dead or resorbed fetuses and number of live fetuses. The live fetuses were weighed, sexed and examined for external anomalies.

The remaining dams (12 /group) were allowed to deliver spontaneously. The number of live/dead pups were recorded, and the live pups were weighed and sexed. On day 4 after birth culling was carried out to make 8 offspring (4 males and 4 f emales). The offspring were reared by the dams until weaning. Following delivery, the dams were checked daily for clinical signs, body weight, food and water consumptions were recorded at various time intervals. On day 21 of post partum all dams were sacrificed and necropsied, and examined as mentioned above. Postnatal body weight changes, food and water consumptions of the pups were recorded until the age of 21 days. During the nursing period the growth and differentiation of the pups were observed, and development parameters were assessed (righting reflex, pinna detachment, tooth-eruption, eyelid separation, visual and auditory function tests, testes descent and vaginal opening). At day 21 of post partum, 1 male and one female from each litter were selected for F1/F2 generation study. At 12 weeks of age they were continuously mated for 14 days. F_1 dams were weighed on days 0, 7, 14 and 20 of gestation. On day 20 of gestation F_1 dams were sacrificed. F_1 dams and F_2 fetuses were examined for abnormalities as mentioned above. This study was not conducted according to FDA guidelines. Our guidelines require that one-half of dams should be sacrificed on day 13 of their respective pregnancies and the remaining dams should be allowed to litter normally.

Results: At the highest dose (30 mg/kg/day), dark purplish-reddening, necrosis and sloughing were seen at the injection sites. No significant effects on body weight gains and food consumptions were seen in treated rats. The estrous cycle of the female rats revealed no differences between the control and treated groups and mated within the first 4 days of pairing. Mating performance, conception rate and fertility index were comparable in all groups. During the gestation period the body weight gains were similar in all groups.

Dams Sacrificed at Day 20

There were no significant changes in pregnancy parameters (corpora lutea, total implants, pre- and post implantation loss, number of live/dead fetuses, litter size, sex ratios, and mean fetal weights). No treatment related external anomalies were seen in live fetuses.

Dams allowed to deliver: No significant differences in the gestation period between the groups were noted. The number of implantation sites, post-implantation survival, litter size, sex ratios, viability and pups weights throughout lactation period were not affected by the treatment. Postnatal development and differentiation were comparable in all groups. There was no significant effect on fertility test and mating performance test of F_1-generation rats. No drug related effects were seen in the F_2 fetuses except anal atresia and anury was seen in 1 fetus of high dose group.

According to sponsor oral administered drug solution are unstable at gastric pH. In the initial submission, in some of the studies E3810 was given along with 1% $NaHCO_3$ to increase the stability of the drug in acidic environment of the stomach. In some of the other toxicity studies access to food was restricted to "accelerate gastic emptying at the time of dose administration so as to maximise systemic absorption of the unchanged drug". Sponsor further stated that "deprivation of food" prior to dose administration will adversly affect lactation and the duration of estrus and will make the interpretation of the results of Segment I fertility and general reproductive performance study difficult. Therefore i.v. route for drug administration was chosen in this study. In this study no information of the pH of the drug solution was given. The proposed clinical route of administration is oral therefore sponsor should have used oral route of administration and drug should have been given along with 1% $NaHCO_3$ (alkalization of the drug solution will stabilized the drug in normal gastic pH and will also remove the need of accelerating gastric empting by "deprivation of food"). Overall study is acceptable. There were no abnormal effects on the fertility and mating performance of the treated male and female rats at i.v. doses up to and including 30 mg/kg/day of E3810.

A Segment II Intravenous Teratological Study of E3810 in Rats (R00295)

Testing Laboratory: [redacted]

Study Start and Completion Dates: March 20, 1995 and February 9, 1996

GLP and QAU Compliance Statement: Sponsor included a statement of compliance with GLP regulation and a quality assurance statement.

Animals: Females (228±14 g, ~8 weeks old) Crj:CD®(SD) rats

Methods: The previous oral Segment II teratological study in rats was not acceptable since the dams were given food for only 5 hours daily during pregnant days 0-16 (study #884212). Sponsor was asked to repeat the Segment II teratological study in rats (see Division letter dated November 10, 1993) and it was agreed that i.v. route was used (see pharmacology review dated February 3, 1995 of amendment #078 of IND [redacted]. In the current study, pregnant female rats were treated with E3810 intravenously at 0, 5, 25 and 50 mg/kg/day on Gestation Days 6 through 17. All dams

were observed daily for clinical signs of toxicity and mortality. Body weights and food consumption were recorded daily. All pregnant rats were sacrificed on Gestation Day 20 for assessment of fetal viability, weight and morphology.

Results: One mid dose animal was found dead on gestation day 2 before the treatment started. Irritation at the injection site (bruise, scab and ulceration) was noted in the mid and high dose groups. Two high dose animals were immobile immediately after dosing and returned to normal within 1 hour. In dams, there were no treatment related changes in body weight, food consumption and number of corpora lutea and implantations. The thymus weight was lower in the mid (35.3%) and high (56.8%) dose groups as compared to the control. Fetal examination did not reveal any significant treatment related changes in number of dead and live fetuses, body weight of the live fetuses, placental weight and sex ratio. This information was summarized in the following table.

Parameter	Control	Low dose	Mid dose	High dose
Total female				
# corpora lutea	16.09	16.05	15.70	15.63
Preimplantation loss	1.18	0.82	0.57	0.78
postimplantation loss				
total	1.18	1.36	0.96	0.71
early resorption	1.18	1.36	0.91	0.67
late resorption	0.00	0.00	0.04	0.04
Live fetus/liter	13.77	13.95	14.22	14.50
% males	52.33	54.88	53.48	52.99
fetal weight (g)	3.99	4.05	3.89	3.87

The incidence of incomplete ossification of parietal bone was increased in the mid (12/156) and high (15/167) dose groups as compared to the control (5/145). The incidence of incomplete ossification of the occipital bone was increased in the high dose group (17/167) as compared to the control (3/145). There were no treatment related changes in the major malformations. One fetus each in the low and mid dose groups had multiple malformations. The results of developmental anomalies were summarized in tables 10 and 11. These tables are attached below.

Table 10. Developmental Anomalies.

DEVELOPMENTAL ANOMALIES IN FETUSES OF FEMALE RATS GIVEN INTRAVENOUS DOSES OF LY307640 SODIUM.
STUDY R00295

	TREATMENT GROUP			
	00	01	02	03
EXAMINATION TYPE	CONCEPTUSES(LITTERS) EXAMINED			
EXTERNAL	303(22)	307(22)	327(23)	349(24)
VISCERAL	158(22)	160(22)	171(23)	181(24)
SKELETAL	145(22)	147(22)	156(23)	167(24)

NOTE: LIVE AND DEAD FETUSES, LATE RESORPTIONS, NEONATES, DELIVERED AND ABORTED LATE RESORPTIONS, AND ABORTED FETUSES WERE GIVEN EXTERNAL EXAMS. DEAD FETUSES AND APPROXIMATELY ONE-HALF OF THE LIVE FETUSES WERE GIVEN SKELETAL EXAMS; THE REMAINING LIVE FETUSES WERE GIVEN VISCERAL EXAMS.

Table 10 (Continued). **Developmental Anomalies.**

DEVELOPMENTAL ANOMALIES IN FETUSES OF FEMALE RATS GIVEN INTRAVENOUS DOSES OF LY307640 SODIUM.
STUDY R00295

	TREATMENT GROUP			
	00	01	02	03
MALFORMATIONS	CONCEPTUSES(LITTERS) AFFECTED			
EXTERNAL				
ABDOMEN-BODY WALL-VISCERAL ORGANS-PROTRUDING	0(0)	1(1)	0(0)	0(0)
HEAD/NECK-CRANIUM-ENLARGED	0(0)	1(1)	0(0)	0(0)
HEAD/NECK-FACE-CLEFT	0(0)	1(1)	0(0)	0(0)
HEAD/NECK-JAW-ABSENT	0(0)	0(0)	1(1)	0(0)
HEAD/NECK-MOUTH-SMALL	0(0)	0(0)	1(1)	0(0)
WHOLE BODY-EDEMA	0(0)	0(0)	0(0)	1(1)
VISCERAL				
DIGESTIVE SYSTEM-TONGUE-SMALL	0(0)	0(0)	1(1)	0(0)

Table 10 (Continued). **Developmental Anomalies.**

DEVELOPMENTAL ANOMALIES IN FETUSES OF FEMALE RATS GIVEN INTRAVENOUS DOSES OF LY307640 SODIUM.
STUDY R00295

	TREATMENT GROUP			
	00	01	02	03
DEVIATIONS	CONCEPTUSES(LITTERS) AFFECTED			
EXTERNAL				
EXTREMITY-FORELIMB-HEMATOMA	0(0)	0(0)	1(1)	0(0)
EXTREMITY-HINDLIMB-HEMATOMA	0(0)	0(0)	2(1)	2(2)
HEAD/NECK-HEMATOMA	8(7)	7(6)	4(4)	6(6)
VISCERAL				
ENDOCRINE SYSTEM-ADRENAL-DARK	3(3)	2(2)	4(3)	0(0)
URINARY SYSTEM-KIDNEY-CAVITATION	4(2)	2(2)	10(5)	1(1)
URINARY SYSTEM-URETER-DILATED	1(1)	0(0)	0(0)	1(1)
SKELETAL				
APPENDAGES-FOREPAW-METACARPAL -INCOMPLETE OSSIFICATION	3(1)	2(2)	0(0)	2(2)
APPENDAGES-HINDPAW-METATARSAL -INCOMPLETE OSSIFICATION	1(1)	2(2)	0(0)	0(0)
AXIAL SKELETON-RIB CAGE-RIB-ABSENT	0(0)	0(0)	0(0)	1(1)
AXIAL SKELETON-RIB CAGE-RIB-EXTRA	0(0)	1(1)	1(1)	0(0)
AXIAL SKELETON-RIB CAGE-RIB-FUSED	0(0)	1(1)	0(0)	0(0)
AXIAL SKELETON-RIB CAGE-RIB -INCOMPLETE OSSIFICATION	2(2)	0(0)	0(0)	0(0)
AXIAL SKELETON-RIB CAGE-RIB-THICK	0(0)	0(0)	0(0)	1(1)
AXIAL SKELETON-RIB CAGE-RIB-WAVY	2(2)	1(1)	0(0)	0(0)
AXIAL SKELETON-RIB CAGE-STERNEBRA-BIPARTITE	0(0)	1(1)	0(0)	1(1)
AXIAL SKELETON-RIB CAGE-STERNEBRA-FUSED	0(0)	1(1)	0(0)	1(1)
AXIAL SKELETON-RIB CAGE-STERNEBRA	1(1)	3(3)	0(0)	1(1)

Table 10 (Continued). **Developmental Anomalies.**

DEVELOPMENTAL ANOMALIES IN FETUSES OF FEMALE RATS GIVEN INTRAVENOUS DOSES OF LY307640 SODIUM.
STUDY R00295

	TREATMENT GROUP			
	00	01	02	03
DEVIATIONS	CONCEPTUSES(LITTERS) AFFECTED			
-INCOMPLETE OSSIFICATION				
SKULL-CALVARIA-INTERPARIETAL BONE				
-INCOMPLETE OSSIFICATION	1(1)	4(2)	7(4)	7(5)
SKULL-CALVARIA-OCCIPITAL BONE				
-INCOMPLETE OSSIFICATION	3(3)	8(4)	5(3)	17(10)
SKULL-CALVARIA-PARIETAL BONE				
-INCOMPLETE OSSIFICATION	5(5)	9(4)	12(9)	15(10)
SKULL-NASAL BONE-INCOMPLETE OSSIFICATION	0(0)	1(1)	0(0)	0(0)
SKULL-ZYGOMATIC ARCH-INCOMPLETE OSSIFICATION	5(3)	2(2)	1(1)	1(1)

Table 10 (Continued). **Developmental Anomalies.**

DEVELOPMENTAL ANOMALIES IN FETUSES OF FEMALE RATS GIVEN INTRAVENOUS DOSES OF LY307640 SODIUM.
STUDY R00295

	TREATMENT GROUP			
	00	01	02	03
DEVIATIONS	CONCEPTUSES(LITTERS) AFFECTED			
-INCOMPLETE OSSIFICATION				
AXIAL SKELETON-RIB CAGE-STERNEBRA-MISALIGNED	0(0)	1(1)	1(1)	1(1)
AXIAL SKELETON-VERTEBRAL COLUMN	6(3)	12(5)	8(7)	7(5)
-CERVICAL VERTEBRA-ARCH-INCOMPLETE OSSIFICATION				
AXIAL SKELETON-VERTEBRAL COLUMN	0(0)	1(1)	0(0)	0(0)
-CERVICAL VERTEBRA-RIB-EXTRA				
AXIAL SKELETON-VERTEBRAL COLUMN	1(1)	1(1)	1(1)	0(0)
-CERVICAL VERTEBRA-RIB-RUDIMENTARY				
AXIAL SKELETON-VERTEBRAL COLUMN-LUMBAR VERTEBRA	1(1)	2(1)	0(0)	0(0)
-ARCH-INCOMPLETE OSSIFICATION				
AXIAL SKELETON-VERTEBRAL COLUMN-LUMBAR VERTEBRA	0(0)	1(1)	0(0)	0(0)
-CENTRUM-BIPARTITE				
AXIAL SKELETON-VERTEBRAL COLUMN	0(0)	1(1)	1(1)	0(0)
-PRESACRAL VERTEBRA-EXTRA				
AXIAL SKELETON-VERTEBRAL COLUMN-SACRAL VERTEBRA	1(1)	0(0)	0(0)	0(0)
-ARCH-INCOMPLETE OSSIFICATION				
AXIAL SKELETON-VERTEBRAL COLUMN	1(1)	4(3)	2(2)	0(0)
-THORACIC VERTEBRA-CENTRUM-BIPARTITE				
AXIAL SKELETON-VERTEBRAL COLUMN	0(0)	1(1)	0(0)	0(0)
-THORACIC VERTEBRA-CENTRUM-HEMI				
AXIAL SKELETON-VERTEBRAL COLUMN	0(0)	0(0)	1(1)	0(0)
-THORACIC VERTEBRA-CENTRUM				
-INCOMPLETE OSSIFICATION				
AXIAL SKELETON-VERTEBRAL COLUMN	0(0)	0(0)	1(1)	0(0)
-THORACIC VERTEBRA-CENTRUM-MISSHAPEN				
PELVIC GIRDLE-ILIUM-INCOMPLETE OSSIFICATION	0(0)	0(0)	0(0)	1(1)
PELVIC GIRDLE-ISCHIUM-INCOMPLETE OSSIFICATION	4(1)	3(2)	0(0)	1(1)
PELVIC GIRDLE-PUBIS-INCOMPLETE OSSIFICATION	4(1)	7(5)	1(1)	3(2)
SKULL-CALVARIA-FRONTAL BONE	0(0)	2(2)	0(0)	0(0)

Table 10 (Continued). **Developmental Anomalies.**

DEVELOPMENTAL ANOMALIES IN FETUSES OF FEMALE RATS GIVEN INTRAVENOUS DOSES OF LY307640 SODIUM.
STUDY R00295

	TREATMENT GROUP			
	00	01	02	03
VARIATIONS	CONCEPTUSES(LITTERS) AFFECTED			
SKELETAL				
AXIAL SKELETON-RIB CAGE-RIB-RUDIMENTARY	23(14)	27(13)	21(11)	29(14)

Table 11. **Fetuses with Multiple Malformations.**

FETUSES WITH MULTIPLE MALFORMATIONS FROM FEMALE RATS GIVEN INTRAVENOUS DOSES OF LY307640 SODIUM.
STUDY R00295

TREATMENT GROUP = 00

- NO FETUSES WITH MULTIPLE MALFORMATIONS AT THIS DOSE LEVEL -

TREATMENT GROUP = 01

ANIMAL NUMBER	CONCEPTUS NUMBER	CONCEPTUS STATUS	SEX	RUNT	MALFORMATION
1073	6	LF	M	YES	EXTERNAL-HEAD/NECK-FACE-LEFT-CLEFT
					EXTERNAL-ABDOMEN-BODY WALL-VISCERAL ORGANS-PROTRUDING

TREATMENT GROUP = 02

ANIMAL NUMBER	CONCEPTUS NUMBER	CONCEPTUS STATUS	SEX	RUNT	MALFORMATION
2065	10	LF	F	YES	EXTERNAL-HEAD/NECK-JAW-LOWER-ABSENT
					EXTERNAL-HEAD/NECK-MOUTH-SMALL
					VISCERAL-DIGESTIVE SYSTEM-TONGUE-SMALL

TREATMENT GROUP = 03

- NO FETUSES WITH MULTIPLE MALFORMATIONS AT THIS DOSE LEVEL -

In summary, in the Segment II teratological reproductive toxicity study in rats, E3810 was given to rats intravenously at 0, 5, 25 and 50 mg/kg/day during days 6 through 17. In dams, local irritation at the injection site (mid and high doses), immobility (high dose) and decreased thymus weight (mid and high doses) were noted. The incidences of incomplete ossification of parietal bone (mid and high doses) and of incomplete ossification of the occipital bone (high dose) were increased. There were no treatment related changes in the major malformations. E3810 was not teratogenic in this study.