2.3.2. *In vivo* and *In vitro* Biotransformation of Telmisartan in Rats and Humans. Structure Elucidation of the Main Metabolite (Report #B388, Study #U95-2310)

This non GLP study was conducted by[ ]. Study period is not given, however, the report is dated December 15, 1995.

The following experiments were performed to establish the main metabolite of telmisartan in rats and its *in vitro* formation in human hepatocytes.

Species	Type	N	System	Dose/Conc.	Purpose
rat	*in vivo*	3	bile	1 mg/kg	excretion balance
rat	*in vivo*	3	bile	30 mg/kg	excretion balance, isolation, structure elucidation
rat	*in vitro*	1	liver microsomes	1-100 µM	identity, preliminary *in vitro* kinetics
rat	*in vitro*	1	hepatocytes	5 and 50 µM	identity
man	*in vitro*	2	hepatocytes	5, 30 and 50 µM	identity, preliminary *in vitro* kinetics

Male rats (strain:[ ] weighing between 200 to 250 gm were fasted 12 hr before and until 3 hr after drug administration. Telmisartan (batch #Br 872/26) was dissolved in 0.5 N NaOH. The preparation was diluted with normal saline and the pH was adjusted to 9.5 with 0.5 N HCl. Rats received 1 or 30 mg/kg doses of [^{14}C]telmisartan into the tail vein.

Rat hepatocytes were obtained from a SD rat, 200 gm, fasted overnight. Human hepatocytes were obtained from two female patients undergoing hepatic resection because of hemangioma (no liver disease). Details on the preparation of rat liver microsomes are not presented in the report. For all *in vitro* studies, telmisartan was dissolved with sonification in DMSO.

Results

After i.v. doses of 1 and 30 mg [^{14}C]telmisartan/kg, 71.5% and 67.2%, respectively, of administered radioactivity was excreted in the bile within 6 hours. Telmisartan was extensively metabolized with only small amounts of parent drug observed in the bile (0.6 to 2.3% of dose). The main metabolite was the acylglucuronide of the parent drug, contributing >90% of the radioactivity found in the bile after each of the administered doses. The presence of this glucuronide conjugate was confirmed by electrospray mass spectrometry. The metabolic pattern in bile was nearly independent of dose or collection period.

The *in vitro* experiments (both microsomes and hepatocytes) showed that liver contributes at least partially to the glucuronidation. The chromatographic, enzymatic, and mass spectrometric behavior of the glucuronide isolated from human hepatocytes was identical with the acylglucuronide isolated from rat bile. Preliminary *in vitro* kinetic studies using rat microsomes and human hepatocytes gave evidence that hepatic glucuronidation was saturated at rather low concentrations.

2.3.3. *In vitro* Glucuronidation of Telmisartan by Microsomes of Rat Liver, Kidney and Small Intestine (Report #B630, Study #U96-2561)

This non GLP study was conducted by[ ]between September 1994 and February 1996. The study was performed to evaluate the occurrence and extent of extrahepatic glucuronidation of telmisartan in the rat.

Microsomes from liver, kidney, small intestine and lung were prepared from untreated adult male rats of two strains: Wistar[ ]rats show hereditary hyperbilirubinemia and have a genetic defect in expressing UDP-glucuronosyltransferases of the UGT1 gene family. The stock solution of [^{14}C]telmisartan (lot #Br 872/26 and Ag 66/2) were prepared in DMSO. Glucuronidation of telmisartan was investigated by incubating microsomes prepared from various tissues with [^{14}C]telmisartan (5-100 µM) for 15 min at 37°C. The reaction was stopped and aliquots of the samples were injected into the[ ]system for analysis.

Results

The acyl-glucuronide of [^{14}C]telmisartan was readily formed upon incubation of [^{14}C]telmisartan with microsomes of Wistar rat liver, kidney or small intestine in the presence of UDPGA. The identity of formed acyl-glucuronide was confirmed by comparison with [^{14}C]telmisartan-glucuronide that was isolated from rat bile (see section 2.1.4). In contrast, incubations with microsomes of Wistar rat lung did not exhibit any glucuronidation of [^{14}C]telmisartan. The pH optimum for glucuronidation catalytic activity for the liver and kidney microsomes (pH 5.5-6.0) was markedly different from the pH optimum for microsomes from the intestine (pH 7.0). The rate of glucuronidation increased in a concentration-dependent manner. The glucuronidation followed a one enzyme Michaelis-Menten kinetics. The ratio of V_{max}/K_M [µl/min/mg] indicated that liver microsomes exhibited the highest intrinsic clearance followed by small intestine and kidney (see below table). This was mainly because the affinity of telmisartan was higher for the liver enzyme than for the enzymes from the small intestine and kidney.

Organ	V_{max} (pmol/min/mg)	K_M (µM)	V_{max}/K_M (µl/min/mg)
liver	187	9.7	19.3
kidney	313	52	6.0
intestine	270	27	10.0

Saturation of the intestinal UDP- glucuronyltransferase enzymes (UDPGTs) at higher concentrations of telmisartan in the lumen of the gut may serve as a possible explanation for the non-proportional increase of telmisartan plasma concentrations with increasing dose. Such rapid saturation of intestinal UDPGTs by telmisartan suggests the impact of food or certain food constituents on telmisartan pharmacokinetics. It is concluded that both intestine and liver play a role in the overall glucuronidation of telmisartan. Glucuronidation of telmisartan was not observed in incubation experiments with liver microsomes of Gunn rats. The absence of glucuronidation in liver microsomes of Gunn rats indicated that UDPGTs of the UGT1 family were primarily involved in the telmisartan glucuronide pathway.

2.3.4. Effect of Telmisartan on Cytochrome P-450-Dependent Enzymes in Rats (Report #3790M, Study #U91-0324)

This non-GLP study was conducted by , Dates of study not provided (date of report: March 1991). The study investigated the ability of telmisartan to induce cytochrome P-450-dependent enzyme activity in rat liver microsomes.

Male Wistar rats (strain: , weight: 200-220 gm) were treated orally with 50 mg/kg/day phenobarbital (n=5), 25 mg/kg/day telmisartan (n=3) or vehicle (50% hydroxypropyl-ß-cyclodextrin) (n=6) for three days. A fourth group of rats received 20 mg/kg ß-naphthoflavone (dissolved in sesame oil) (n=4) intraperitoneally for three days. On day 4, the animals were sacrificed and liver microsomes were prepared. Additionally, blood samples were collected from animals receiving telmisartan before sacrifice for the determination of drug concentration by .

Results

The induction of P-450-dependent enzyme activity was measured by monitoring the metabolism of 7-ethoxyresorufin, 7-pentoxyresorufin and 7-ethoxycoumarin. None of the animals treated with telmisartan showed enzymatic activities significantly different from the activity observed in microsomes from control rats. On the other hand, microsomes prepared from rats treated with beta-naphtoflavone potentiated 7-ethoxyresorufin-O-deethylase, as well as pentoxyresurofin and ethoxycoumarin converting activity. Phenobarbital significantly increased 7-ethoxyresorufin-O-deethylase and pentoxyresurofin converting activity but not the metabolism of ethoxycoumarin. The plasma of telmisartan-treated animals showed measurable quantities (3.23 ± 1.56 µg/ml; n = 3; mean ± SEM) of telmisartan.

In conclusion, the data obtained did not demonstrate any evidence for the induction of cytochrome P-450-dependent enzyme activity by oral administration to rats of 25 mg/kg telmisartan for three consecutive days .

2.3.5. Metabolism of [^{14}C]Telmisartan Following Intravenous Administration to Dogs (Report #B783, Study #U97-2276)

This non-GLP study was conducted by( ) between March 1996 and May 1997. The study investigated the metabolite profile and metabolite identification of [^{14}C]telmisartan in beagle dogs.

One anesthetized female (16.3 kg) and one non-anesthetized male (12 kg) beagle dog received single i.v. doses of 1 and 50 mg [^{14}C]telmisartan/kg (batch #Ag 66/2), respectively, at concentrations of 1 and 50 mg/ml, respectively. The dogs were fasted for 22 hr prior to and during the first 2 hr after administration. Telmisartan was dissolved in 0.5 M sodium hydroxide solution, diluted with saline and pH was adjusted with 0.5 M HCl. Bile was collected from the non-anesthetized male dog in fractions at 0-2, 2-4 and 4-6 hr. A single spot sample of bile was obtained by puncture of the gall bladder of the anesthetized female dog 2 hr after i.v. dosing. Blood was collected from the same animal just before the terminal anesthesia at 2 hr after dosing. The 0-6 hr bile fraction from a male dog (non-anesthetized) dosed intravenously (1 mg/kg) in study #U92-0600 (see section 2.1.7) was also investigated, simultaneously, for metabolite pattern.

Results

In general, dogs eliminated the radioactivity from blood into bile very fast. The excretion was 53.8% in 2 hr, 62.3% in 4 hr and 66.1% of the dose in 6 hr (section 2.1.7). However, the radioactivity that was present in the spot sample of bile taken from the anesthetized female dog 2 hr after dosing contained a total of 19.5% of the administered [^{14}C]telmisartan. This suggests that a considerable amount of radioactivity (19.5% *vs.* 53.8%) was already excreted into the gut lumen. Radioactivity in bile samples of male dogs was predominantly (80 to 94% of total sample radioactivity) attributable to the 1-*O*-acylglucuronide of [^{14}C]telmisartan. Several minor radioactive compound peaks were also detected. These consisted of a rearrangement product of the 1-*O*-acylglucuronide, which was formed by non-enzymatic acyl migration (accounting for 1.9 to 3.5% of total sample radioactivity) and another designated glucuronide of telmisartan (accounting for 4.2 to 5.9% of total sample radioactivity). Minor quantities of parent compound, [^{14}C]telmisartan (0.4 to 1.1%), were also detected in bile samples (Table 2.3.5.1).

TABLE 2.3.5.1

RELATIVE AMOUNTS OF [^{14}C] TELMISARTAN AND ITS METABOLITES (% OF TOTAL RADIOACTIVITY), IN BILE SAMPLES OF DOGS AFTER I.V. 1 MG/KG [^{14}C] TELMISARTAN

animal; sample	other metabolites retention time			1-*O*-acyl-glucuronide	gluc. rearrang. product	parent telmisartan	total
	12 min	15.6 min	17.1 min				
1; 0-6 h							
2; 2 h							
mean	2.7	5.1	2.6	87.0	2.7	0.8	100.7

Treatment of bile with ß-glucuronidase resulted in the formation of [^{14}C]telmisartan from the 1-*O*-acylglucuronide of [^{14}C]telmisartan. The study showed that in dogs [^{14}C]telmisartan was metabolized nearly exclusively by conjugation of the parent compound by glucuronic acid. This was in good accordance with the metabolism of telmisartan in rats and humans, where the glucuronidation of the parent compound was the only detectable metabolic pathway. The identity of the major metabolite as the 1-*O*-acylglucuronide was confirmed by [ ] analysis.

The metabolite profile of telmisartan in plasma was investigated in one female dog [ ] analysis of a plasma sample taken 2 hr after dosing showed, in addition to parent compound, the presence of one major metabolite. The retention time of this metabolite was identical to the retention time of the 1-*O*-acylglucuronide of telmisartan. This metabolite accounted for 22% of the total sample radioactivity. Thus smaller amounts of radioactivity were present in plasma that were not attributable to the parent compound but were assigned to the 1-*O*-acylglucuronide of [^{14}C]telmisartan.

2.4. Excretion

Results from all studies concerning excretion except for excretion into milk are summarized in Table 2.4.5.

2.4.1. Excretion Balance of [^{14}C]Telmisartan in Mice (Report #B336, Study #U95-2136)

The summary of this study is given under section 2.1.1. as part of pharmacokinetics.

2.4.2. Pharmacokinetics and Whole Body Autoradiography of [^{14}C]Telmisartan in Male Albino Rats (Report #B54, Study #U92-0466)

The summary of this study is given under section 2.1.2. as part of pharmacokinetics.

2.4.3. Excretion Balance After Oral and Intravenous Administration of [^{14}C]Telmisartan in Dogs (Report #B97, Document #U92-0600)

The summary of this study is given under section 2.1.5. as part of pharmacokinetics.

2.4.4. Transfer of [^{14}C]Telmisartan into Milk in Rats (Report #U96-0196, Study #NBIBC-9621)

The summary of this study is given under section 3.5.6. as part of reproductive toxicity.

TABLE 2.4.5
SUMMARY OF EXCRETION DATA FOR TELMISARTAN (% OF DOSE)

Species	Dose mg/kg/d	Duration	Route	Sex	Urine (+ cage wash)			Feces			Total excretion	Bile 0-6 h	Ref. sec #
					0-24h	0-48h	0-X h	0-24h	0-48h	0-X h			
Mouse	1	single	oral	M	2.80	3.70	4.00 (72h)	58.1	77.9	85.2 (72 h)	89.2 (72 h)		2.1.1
				F	0.60	0.80	1.10 (72 h)	60.9	80.2	87.0 (72 h)	88.1 (72 h)		
Rat	1	single	oral	M	0.07	0.07	0.08 (96 h)	84.3	98.4	99.7 (96 h)	99.7 (96 h)	57.3[a]	2.1.2
			i.v.	M	0.10	0.11	0.12 (96 h)	85.1	98.3	99.5 (96 h)	99.6 (96 h)	82.6	
Rabbit	1	single	oral	F	0.594	0.958	2.15 (96 h)	42.5	86.6	97.9 (96 h)	99.0 (96 h)		2.1.5
Dog	1	single	oral	M+	0.03	0.07	0.10 (96 h)	68.1	86.0	95.8 (96 h)	95.9 (96 h)	-	2.1.7
			i.v.	F[b]	0.12	0.25	0.39 (96 h)	38.4	74.7	94.3 (96 h)	94.7 (96 h)	66.1[c]	
Human	40 mg	single	oral soln	M			0.49 (120 h)			97.0 (120 h)	>90 (120 h)		study #502.110

a: i.d. administration; b: mean from 2 male and 2 female dogs; c: one male dog

3. TOXICOLOGY

For all toxicological studies, the formulation of telmisartan for oral administration was a suspension in 0.5% hydroxyethylcellulose administered in a volume of 5-10 ml/kg. For intravenous studies, test substance was dissolved in NaOH by brief sonication, followed by dilution with normal saline and pH adjustment to 8.9 - 9.5 with HCl.

3.1. *Acute Toxicity Studies*

3.1.1. Acute Oral Toxicity Study in Rats (Study #26R, Report #U92-0638) Vol. 24

This GLP study was conducted by( ) between June 23 and July 7, 1992.

Three male and three female rats( ) 43 days of age and weighing 137-166 gm, received single 2000 mg/kg oral doses of telmisartan (batch #8230151).

All animals were observed at least twice a day for mortality and drug effects for 14 days following treatment. Body weights were recorded on days 1, 2, 7, and 14. Necropsies were performed at the end of the observation period; histopathological examinations were not performed.

No animals died. No clinical signs of toxicity were observed and no gross lesions were seen during the necropsy of the animals.

3.1.2. Acute Intravenous Toxicity Study in Rats (Study #07R, Report #U92-0300) Vol. 17

This GLP study was conducted by[redacted] between February 14 and March 4, 1992.

Groups of three albino rats [redacted] age: 6-7 weeks, weight range: 140-180 gm) per sex were given telmisartan (batch #8110130) at single intravenous doses of 150 (males only), 200, 250 or 300 mg/kg at an infusion rate of 1.5 ml/min (10 mg telmisartan /ml). A fifth group received vehicle (solution containing NaOH, NaCl and pH adjusted to 8.9 with HCl) only. All animals were observed for a period of two weeks without treatment. The overall appearance and behavior of each animal were observed at least twice a day. Body weights were determined on the day of administration (day 1), as well as on days 2 to 7 and 14 of the experiment. Food and water consumption were not determined. All animals were necropsied; histopathological examinations were not performed.

Results

Immediately after the iv. injection, all male animals dosed at 150 mg/kg showed salivation, followed by prone position, ptosis, and slight cyanosis. Four hours after administration they were normal, and they remained normal until the end of the recovery period.

The first signs after administration of 200 mg telmisartan /kg in both males and females were apathy, prone position, decreased breathing frequency and cyanosis. Peripheral vasodilation was clearly visible in all animals. One male was found dead the following morning. A second male showed piloerection, abdominal position, and hypothermia on day 2 and was found dead on day 3. The remaining male and all three females showed piloerection on the day following injection, but recovered before the end of the experiment.

In all animals dosed at 250 mg/kg, apathy, prone and lateral position, decreased breathing frequency and cyanosis were observed immediately after dosing. Vasodilation of peripheral blood vessels and tonic-clonic convulsions also occurred in these animals. All females and two males died within 2 hours after administration. The remaining male was found dead the following morning.

In all animals dosed at 300 mg/kg the signs were the same as in the 250 mg/kg group, but the animals died within 40 minutes of administration of telmisartan. Table 3.1.2.1 summarizes the mortality data.

The body weight gain of animals given 150 mg/kg was comparable to that of controls. Reduced body weight gain was observed in female rats and the single surviving male given 200 mg/kg. All four animals regained their values at the end of the recovery period.

At necropsy, the animals given 300 mg/kg showed serosanguineous pulmonary edema and congestion of parenchymal organs (all rats), as well as petechial hemorrhages of the thymus (2 rats) and hemorrhagic erosions of the stomach (one rat). Comparable macroscopic findings were observed in the rats given 250 mg/kg; 4 of 6 rats had petechial hemorrhages of the thymus, 4 of 6

showed serosanguineous pulmonary edema, one male had hemorrhages in the lung, and all animals had hemorrhagic erosions of the stomach. Rats dosed at 200 mg/kg and sacrificed at term showed pale kidneys (two rats) and diffuse red brown discoloration of the kidneys (1 female). Organs of animals in the low dose and control groups were not remarkable. Deaths in this study were attributable to circulatory collapse due to exaggerated hypotensive activity of the test substance at the high doses used.

This study establishes a nonlethal dose of 150 mg/kg and minimum lethal dose of 200 mg/kg in rats. The sponsor estimates an approximate median lethal dose between 150 and 200 mg/kg for males and between 200 and 250 mg/kg for females.

TABLE 3.1.2.1.
MORTALITY IN RATS AFTER SINGLE INTRAVENOUS DOSES OF TELMISARTAN

Dose mg/kg/day	N/sex	Deaths within				
		6 hr	7-24 hr	2-7 days	8-14 days	Total
150	3M	0	0	0	0	0
200	3M/3F	0/0	1/0	1/0	0/0	2/0
250	3M/3F	2/3	1/0	0/0	0/0	3/3
300	3M/3F	3/3	0/0	0/0	0/0	3/3

3.1.3. Acute Oral Toxicity Study in Dogs (Study #43R, Report #U92-0780) Vol. 25

This GLP study was conducted by[redacted] between September 1 and 21, 1992.

Groups of one male (12.4-12.8 kg) and one female (12.2-12.7 kg) beagle dog, 14-16 months of age, were given telmisartan (batch #120595) orally by gavage (10 ml/kg) at single doses of 1000 or 2000 mg/kg.

All animals were observed at least twice a day for mortality and drug effects for 14 days following treatment. The body weights were recorded on days 1, 8, and 15. Autopsies were not performed.

No animals died. The only drug-related clinical sign observed was white discoloration of the feces, which was noted at both doses for up to 3 days postdosing in some animals. A slight decrease in food consumption with no influence on body weight gain was observed in one high dose female. The approximate median lethal dose (ALD_{50}) of telmisartan following oral administration to dogs was higher than 2000 mg/kg.

3.2. *Subchronic and Chronic Toxicity Studies*

3.2.1. One Month Oral Toxicity Study in Rats (Study #90Q, Report #U92-0332) Vol. 17-19

This GLP study was conducted by

between October 14 and December 1, 1991.

Male and female albino rats were approximately 46 days of age and weighed 219-221 gm (males) or 170-185 gm (females) at the start of the study. Telmisartan (batch #8110110) was administered once daily for 28 days at doses of 10, 50, 100 or 200 mg/kg by oral gavage. The control group received the vehicle. Each group consisted of 10 male and 10 female rats. The high dose and control groups contained an additional 10 males and 10 females for a five weeks recovery phase without dosing. In addition, three satellite animals per dose per sex (no control) were used for drug plasma concentration determinations performed before dosing and 1, 2, 4, 7 and 24 hr post-dosing on days 1, 14 and 28. The doses were selected on the basis of a two week oral dose-range finding study in which dosages of 125 to 1000 mg/kg/day caused decreased body weight gain and food consumption as well as increased BUN and creatinine values. Gastric ulcers and erosions at 500 and up mg/kg, and biochemical evidence of hepatic damage at 1000 mg/kg were also evident. Histopathological changes (focal inflammations, ulcers) were observed in the gastric mucosa of the 500 and 1000 mg/kg groups. Thus in the current study, it was anticipated that a high dose of 200 mg/kg would cause biochemical and pathological evidence of target organ toxicity in the kidney, gastric ulcers and erosions. The low dose of 10 mg/kg/day was approximately 30 times a pharmacologically active oral dose of 0.3 mg/kg in the renal hypertensive rat and 10-times a pharmacologically active oral dose of 1 mg/kg in angiotensin II pressor response models. The mid and mid-high doses of 50 and 100 mg/kg were selected to investigate the dose-response for toxic effects.

All animals were observed once daily during the pretest period and twice daily during the administration period. The body weight and food and water intake of each animal was determined once a week before and during the dosing period. Hematology and clinical chemistry parameters were examined from blood samples collected from all animals in week -1 and in the 4th week of the study. For toxicokinetics study, blood samples were collected from 3 animals/sex/group, at 0, 1, 2, 4, 7 and 24 hr after the first dose (day 1); 1, 2, 4, 7 and 24 hr after the 14^{th} dose (day 14) and 1, 4, 7 and 24 hr after the 28^{th} dose (day 28). The recovery animals were also tested in the 9th week of the study. Urinalysis was performed in study weeks 3 and 9 (recovery). At the end of the administration and recovery periods, all animals (except toxicokinetic group) were subjected to a complete necropsy that included weighing of selected organs and a complete histopathological evaluation (Table 3.2.1.1).

Results

One high-dose male rat assigned to the toxicokinetic group had to be killed (after day 15, details not given) because of its bad condition. There were no other deaths or unscheduled sacrifices. Mean body weight gain (%) was slightly and dose-dependently decreased in all treated male groups compared to the controls, the difference being significant at 100 and 200 mg/kg/day. No

weight decrease was found in females. A significant decrease in food consumption was observed only among high dose males throughout the treatment period. This effect was reversed during the recovery period. A significant increase in water consumption, which was not strictly dose-dependent, was noted in all drug treated males during the dosing period.

TABLE 3.2.1.1.
TISSUES/ORGANS SAMPLED FOR HISTOPATHOLOGICAL EXAMINATION

Adrenals*
Aorta
Bone marrow
Brain*
Cecum
Colon
Duodenum
Epididymides
Esophagus
Eyes with optic nerves
Femur
Heart*
Ileum
Jejunum
Kidneys*
Lachrymal glands
Liver*
Lungs*
Lymph nodes -mesenteric
-neck region
Macroscopical lesions
Mammary glands
Ovaries*
Pancreas
Parotid glands
Pituitary*
Prostate
Rectum
Seminal vesicles
Submandibular salivary glands
Sublingual salivary glands
Sciatic nerve, peripheral
Skeletal muscle
Skin
Spinal cord
Spleen*
Sternum
Stomach
Testes*
Thymus*
Thyroid* with indent
parathyroid
Tongue
Trachea
Urinary bladder
Uterus

* organ weighed

A slight but significant, reversible reduction in red blood cell count, hematocrit and/or hemoglobin was observed in all drug treated groups, but no correlating alterations in bone marrow were detected. Also, a significant reduction in thromboplastin time, as compared to the controls, was found in males and females given 50 or more mg/kg/day. Significant elevations in BUN (1.5- to 2.5-fold) and creatinine, compared to control values, were noted in all treated groups; males were more affected than females. These were not dose-dependent and completely reversible. Increased cholesterol ($P < 0.01$) in males given 50 or more mg/kg/day and decreased glycerol ($P < 0.05$) in all the treated males were noted but the changes in glycerol were not dose-related. Both effects were reversible. At the end of the study a slight increase ($P < 0.05$ to 0.01) in potassium was found in all treated males and in the females of groups given 50 or more mg/kg/day, and a slight increase in magnesium ($P < 0.01$) was found in males and females of groups given 100 and 200 mg/kg/day. These findings were not dose-dependent and completely reversible. Reversible decreases ($P < 0.05$) in urine volume and increases in specific gravity occurred only in males given 50 or more mg/kg/day.

The mean absolute and relative (% of body weight) weights of the following organs from drug-treated groups were significantly ($P < 0.05$-0.01) different from the corresponding control values:

increased: *kidney* females given 10 and 100 mg/kg/day
adrenals high dose male recovery group
pituitary high dose male recovery group

decreased: *heart* 100 and 200 mg/kg/day males; females in all treated groups
pituitary females in groups given 10, 100 and 200 mg/kg/day
thyroid high dose females

Drug treatment-related gross pathological findings were limited to single mucosal erosions of the stomach. The group-distribution was as follows:

0 mg/kg/day: 0/10 males, 0/10 females
50 mg/kg/day: 2/10 males, 2/10 females
100 mg/kg/day: 5/10 males, 2/10 females
200 mg/kg/day: 4/10 males

Under light microscopy, dose-related pathology was observed in the glandular stomach, the liver and the kidneys of male and female animals. Evidence of erosions and ulcers of the mucosa of the glandular stomach was found in animals of all dose groups. The incidence is summarized in table 3.2.1.2. Gastric mucosal changes appeared to be reversible as only marginal inflammatory changes were detected in 3/10 high dose male rats of the recovery group. Drug exposure was associated with a patch-like cytoplasmic basophilia of centrilobular hepatocytes. This alteration was found in males at 50 mg/kg, females at 100 mg/kg, and males and females at 200 mg/kg. It was not seen in high dose rats sacrificed five weeks after drug withdrawal. Renal pathology consisted of hyperplasia of the epithelioid cells of the juxtaglomerular apparatus, with prominent granularity in males at all dose levels and in females given doses of 50 mg/kg or more. This finding, which was more pronounced in males than in females, regressed after the five week drug withdrawal period.

TABLE 3.2.1.2.

INCIDENCE OF GASTRIC AND DUODENAL LESIONS OBSERVED MICROSCOPICALLY IN A 4-WEEK ORAL TOXICITY STUDY OF TELMISARTAN IN RATS

Histopathologic Finding:	Dosage (mg/kg/day)									
	0		10		50		100		200	
	m 10	f 10	m 10	f 10	m 10	f 10	m 10	f 10	m 10	f 10
No significant changes	10	10	9	9	7	8	2	7	0	5
Inflammation/fibrosis only	0	0	0	0	0	1	3	1	5	3
Erosion (with or without infl.)	0	0	1	1	3	1	5	2	4	2
Ulcer (with or w/o erosion, infl.)	0	0	0	0	0	0	0	0	1	0
Total with mucosal injury	0	0	1	1	3	2	8	3	10	5

Plasma concentrations of telmisartan were measured in 3 male and 3 female rats per dose level on days 1, 14 and 28. The time to peak (Tmax) was in the range of 1-24 hr (median 1 hour). Cmax and $AUC_{0\text{-}24hr}$ showed dose-dependent increases with increasing dose which were not strictly dose-proportional. After repeated doses of 100 or 200 mg/kg/day, a trend to higher values on days 14 and 28 than on day 1 was noted in both sexes (Table 3.2.1.3). Due to the high interindividual variabilities (large standard deviation) in plasma concentrations, no statistically significant differences in Cmax and AUC between males and females could be observed.

TABLE 3.2.1.3
PEAK PLASMA CONCENTRATIONS AND AUCs OF TELMISARTAN IN A 4-WEEK ORAL TOXICITY STUDY IN RATS

Dose		N	Cmax (µg/ml)				AUC (µg.h/ml)			
			Male		Female		Male		Female	
(mg/kg/d)	Day	M/F	Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD
10	1	3/3	0.4	0.1	0.3	0.2	4.2	0.4	2.7	1.9
50	1	3/3	3.5	2.2	1.9	0.7	20.2	2.7	17.1	3.2
100	1	3/3	26.6	29.5	24.7	14.4	115.5	111.5	89.6	48.8
200	1	3/3	28.1	18.0	68.9	55.0	212.8	98.3	186.2	144.5
10	14	3/3	0.4	0.1	0.5	0.2	5.5	0.7	6.8	3.5
50	14	3/3	4.2	1.3	2.4	2.2	25.9	4.4	20.7	9.3
100	14	3/3	37.3	25.1	53.5	15.7	246.4	230.5	158.9	22.4
200	14	3/3	74.7	13.3	49.0	35.9	750.8	467.7	275.1	209.7
10	28	3/3	0.3	0.1	0.4	0.3	3.7	0.9	5.4	3.3
50	28	3/3	2.5	2.5	3.0	1.7	22.2	17.3	35.4	21.2
100	28	3/3	53.6	21.8	42.5	25.4	271.5	94.1	173.9	50.4
200	28	3/3	78.8	29.8	50.6	17.5	858.9	138.3	411.9	268.3

In conclusion, the study fails to establish a no observed adverse effect level. According to the sponsor, the lowest dose of 10 mg/kg was regarded as a "minimally toxic dose".

3.2.2. One Month Oral Toxicity Study in Male Rats With Saline Supplementation (Study #09R, Report #U93-0002) Vol. 27

This GLP study was conducted by

between April 8 and May 5, 1992. A previous toxicity study (Study #90Q, section 3.2.1) showed a spectrum of adverse findings which were largely attributed to exaggerated pharmacological effects of the test substance at high doses in normotensive rats. Since a positive sodium balance down regulates the RAAS, side effects due to angiotensin II receptor blockade by telmisartan should be prevented by saline supplementation in place of drinking water.

Male albino rats were approximately 48 days of age and weighed 250-285 gm at week -2 of the study. Two groups of 10 rats each were given telmisartan (batch #81101170) at repeated oral gavage doses of 100 mg/kg for 28 days. Two groups of 10 rats each received vehicle and served as controls. One control group and one drug-treated group received 0.9% NaCl instead of drinking water; the remaining two groups received normal tap water. Male rats were used because they were more sensitive to the test substance than females in previous toxicity studies.

All animals were observed twice daily. The body weight and food and water (or NaCl solution) intake of each animal were determined once a week before and during the dosing period. Animals were also weighed before necropsy. Hematology and clinical chemistry parameters were examined from blood samples collected in week -2 and in the 4th week of the study. Blood samples for the plasma renin assay were taken from 5 animals per group in the 4th week of the study. Urine aldosterone levels were determined on 24 hour urine samples from 5 rats per group on the day after the last administration of telmisartan. A complete necropsy that included weighing of heart, liver, kidneys and adrenals was performed on all animals. Heart, liver, kidneys, stomach with duodenum and organs with macroscopical alterations were examined histopathologically.

Results

No deaths occurred. The only clinical sign observed was increased motor activity from week 2 onwards in both drug treated groups. Decreased body weight gain and food consumption were noted only in animals receiving test substance and normal drinking water. Animals which received saline instead of tap water showed a conspicuously increased food intake compared to those rats given normal drinking water. Saline intake increased in both control and telmisartan-treated groups from week -1 until the end of the study (Table 3.2.2.1).

TABLE 3.2.2.1
EFFECTS OF ORAL SALINE SUPPLEMENTATION: BODY WEIGHT AND FOOD AND WATER/SALINE INTAKE

Group		G0	G1		G2		G3	
Dose (mg/kg/day)	wk	0	0		100		100	
Water/0.9% NaCl		water	0.9% NaCl		water		0.9% NaCl	
Parameter			Δ%		Δ%		Δ%	
Body weight	-1	301.7	301.7		301.8		304.3	
(grams)	1	324.3	321.7		309.1*	4.7	326.5	
	2	345.3	342.3		318.4*	7.8	348.6	
	3	365.2	361.3		327.6*	10.3 ↓	365.8	
	4	377.4	377.1		333.9*	11.5 ↓	378.8	
BW gain (% wk -1)	4	125.1	125.0		110.6*	11.6 ↓	124.4	
Food intake (g/wk)	-1	189.8	191.9		190.2		191.5	
	1	186.0	185.4		167.1*	10.2 ↓	186.7	
	2	184.7	184.0		158.6*	14.1 ↓	184.1	
	3	180.6	179.8		160.8*	11.0 ↓	179.6	
	4	177.4	179.3		153.4*	13.5 ↓	177.6	
Water/saline intake	-1	253.5	351.1*	38.7 ↑	242.7		356.3*	40.6 ↑
	1	245.2	335.0*	36.6 ↑	246.9		331.2*	35.1 ↑
	2	232.8	338.3*	45.3 ↑	289.4*	24.3 ↑	337.0*	44.8 ↑
	3	231.2	327.6*	41.7 ↑	280.8*	21.5 ↑	314.1*	35.9 ↑
	4	231.8	334.5*	44.3 ↑	286.1*	23.4 ↑	319.6*	37.9 ↑

* Statistically significant ($p < 0.05$) compared to G0
Δ% % difference compared to G0
↓ Toxicologically meaningful decrease
↑ Toxicologically meaningful increase

Significant ($P < 0.05$ to 0.01) decreases in RBC count, hemoglobin and hematocrit and increased urea nitrogen and creatinine, as well as increased serum total cholesterol, potassium and magnesium and decreased sodium and calcium were noted in drug treated animals receiving normal drinking water. In the drug-treated group given saline instead of tap water, decreases ($P < 0.05$ to 0.01) in RBC and calcium and increases in potassium were observed. Plasma renin activity was elevated in both groups given drug; the effect was found to be more pronounced in animals having received saline as drinking solution. Low urinary aldosterone levels (in some cases below quantifiable level) were observed in all samples (Table 3.2.2.2). No difference was observed between drinking water and NaCl control groups.

TABLE 3.2.2.2
EFFECTS OF ORAL SALINE SUPPLEMENTATION: CLINICAL PATHOLOGY

Group		G0	G1		G2			G3		
Telmisartan (mg/kg)		0	0		100			100		
Drinking water/Saline		Water	Saline		Water			Saline		
No. Animals/Group		10M	10M		10M			10M		
Parameter	units	value	value	%#	value	%		value	%	
Hematology										
RBC	$10^6/mm^3$	7.9	7.8		7.20**	-8.9		7.6**	-3.8	
HCT	vol%	47.3	47.1		42.60**	-9.9	↓	46.3		
Hb	g/dl	15.8	15.7		14.10**	-10.8	↓	15.5		
Clinical Chem.										
Urea Nitrogen	µmol/l	8.3	7.5		18.30**	+120	↑	8.3		
Creatinine	µmol/l	45.4	44.5		49.20**	+9.3	T	44.2		
Cholesterol	mmol/l	1.71	1.82		2.29**	+33.9	↑	1.90		
Calcium	mmol/l	2.78	2.82		2.65**	-4.7		2.70*	-2.9	
Potassium	mmol/l	4.38	4.60		5.61**	+28.1	↑	4.75*	+8.4	
Sodium	mmol/l	144.1	142.2**	-1.3	140.00**	-2.8		141.2**	-2.0	
Magnesium	µmol/l	783.0	755.0		940.20**	+20.0	↑	756.6		
Special studies										
PRA	AI/ml/h	13.8	13.2		21.00**	+52.0	↑	33.7**	+144	↑
Urine Aldosterone	pmol/l	40.0	38.3		22.00§	-45.0	↓	BLQ		↓

§ Data from one animal; all others in this group and G3 below limits of quantitation (BLQ) of 16 pmol/l
* Statistically significant ($p < 0.05$) compared to G0
** Statistically significant ($p < 0.01$) compared to G0
# % difference compared to G0
↓ Toxicologically meaningful decrease
↑ Toxicologically meaningful increase
T Trend

Relative and absolute heart and absolute liver weights were clearly decreased in drug treated animals receiving normal drinking water ($P < 0.01$), while only a slight trend to decrease in heart weight ($P > 0.05$) was apparent in the drug treated group supplemented with saline. Relative adrenal and kidney weights showed increases ($P < 0.01$) in the drug-treated group given normal drinking water. In the same group, 8 of 10 rats had gastric ulcers/erosions and/or submucosal inflammation indicative of gastric mucosal injury. Hypertrophy/hyperplasia of the juxtaglomerular apparatus of the kidney was present in both treated groups; however, the change was less prominent in the saline-supplemented group (Table 3.2.2.3). Degree of granularity of the afferent arterioles and interlobular arteries, in particular, was less pronounced in the drug treated animals receiving saline. This was attributed to down regulation of RAAS by positive sodium balance.

TABLE 3.2.2.1
EFFECTS OF ORAL SALINE SUPPLEMENTATION: POST-MORTEM FINDINGS

Group		G0	G1		G2		G3
Dose telmisartan (mg/kg)		0	0		100		100
Drinking water/Saline		Water	Saline	%#	Water	%	Saline
No. Animals/Group		10M	10M	diff	10M	diff	10M
Heart weight	g	1.09	1.10		0.87**	(-20.0)↓	1.03
	%BW	0.30	0.30		0.27**	(-10.7)↓	0.28
Kidney weight	g	2.50	2.65**	(+6.0)	2.56		2.63
	%BW	0.68	0.73**	(+6.3)	0.78**	(+13.9)↑	0.71
Liver weight	g	14,16	14.01		12.08**	(-14.7)	14.27
	%BW	3.86	3.82		3.70	(+4.0)	3.83
Adrenal weight	mg	81.40	84.50		88.90		79.30
	%BW	22.20	23.10		27.30**	(+22.9)↑	21.50
Gastric ulcers/erosions		none	none		8.00		none
JG hypertrophy/hyperplasia		-	-		+++		++

\+ = minimal, ++ = mild, +++ = moderate
* Statistically significant ($p < 0.05$) compared to G0
** Statistically significant ($p < 0.01$) compared to G0
\# % difference compared to G0
↓ Toxicologically meaningful decrease
↑ Toxicologically meaningful increase

In conclusion, supplementation with normal saline in the present study largely prevented the renal and gastric side effects observed in rats after 4-weeks of treatment with telmisartan. Additionally, saline supplementation prevented decreased body weight gain and food consumption, reduced red blood cell indices, increased BUN, creatinine, cholesterol, potassium and magnesium. In contrast, JG hypertrophy/hyperplasia was still present in both treated groups, but the degree of change was less pronounced in the saline supplemented group compared to the group receiving drug and drinking water. Saline supplementation, however, had no effect on the drug-induced plasma renin increase and aldosterone decrease.

3.2.3. One Month Intravenous Toxicity Study in Rats (Study #19R, Report #U93-0333) Vol. 28-29

This GLP study was conducted by

between June 3 and June 30, 1992.

Male and female albino rats were approximately 69 days of age and weighed 292-358 gm (males) or 177-231 gm (females) at the start of the study. Telmisartan (batch #8110130) was administered iv. once daily for 28 days at doses of 0.1 (0.1 mg/5 ml), 2 (2 mg/5 ml), or 20 (20 mg/5 ml) mg/kg at approximately 10 ml/min. The control group received the vehicle (5 ml/kg). Each group consisted of 10 male and 10 female rats. The high dose and control groups contained an additional 10 males and 10 females for a six weeks recovery phase without dosing. In addition, three satellite animals per dose per sex (no control) were used for drug plasma concentration determinations performed before dosing and 5 min, 30 min and 1, 4, 7 and 24 hr post-dosing on days 1 and 28. Test substance was dissolved in 1 N NaOH by brief sonication. The preparation was diluted with normal saline and the pH was adjusted to 9.5 with 1 N HCl. The doses were selected on the basis of a two week iv. dose-range finding study in which dosages of 25 to 100 mg/kg/day were associated with renal functional changes and gastric lesions. Thus, 20 mg/kg was selected as the high dose. 0.1 mg/kg was selected for the low dose because iv. administration of the test substance at this dose effectively antagonized the pressor response in rats administered angiotensin II in pharmacological models. The mid dose of 2 mg/kg was expected to define the threshold for adverse side effects.

All animals were observed twice daily during the administration period. The body weight and food and water-intake of each animal was determined once a week before and during the dosing period. ECGs were done pretest and 0.5 and 3 hr after dosing during weeks 1 and 4 on all animals and once during week 9 for recovery animals. Hematology and clinical chemistry parameters were examined from blood samples collected in week -2 and in the 4th week of the study. Urinalysis was performed in study weeks 3 (males) and 4 (females). The recovery animals were also tested in the 10th week of the study. Plasma renin activity and aldosterone were measured in blood samples taken from 5 males and 5 females of each group at the end of the administration period. At the end of the study, all animals were subjected to a complete necropsy that included weighing of selected organs. All tissues from high dose and control animals were examined histopathologically, as were target organs and tissues showing macroscopical changes from animals in the low and mid dose groups (Table 3.2.3.1).

Results

No animals died during the study. A significantly lower body weight was recorded for the males given 20 mg/kg at the end of week 4 (mean difference of 7.3% compared to controls) and at the first recovery week (5.5%). A significant decrease in food intake was noted for this group. The water intake was significantly increased in the high dose males (week 2-4) and females (week 2-5). A significant increase in heart rate was observed during the dosing period only in week 1 in mid (+4%) and high (+11%) dose group animals.

TABLE 3.2.3.2.
ORGAN WEIGHTS IN A 4-WEEK INTRAVENOUS TOXICITY STUDY OF TELMISARTAN IN RATS

	Males				Females			
Dose (mg/kg)	0	0.1	2	20	0	0.1	2	20
Body Weight (g)⊗	386.2	362.7*	365.1*	353.4*	238.1	232.7	234.0	228.8
Heart absolute (g)	1.23	1.17	1.11*	1.01*	0.90	0.87	0.87	0.76*
rel./BW (%)	0.32	0.32	0.31	0.29*	0.38	0.37	0.37	0.33*
Kidney Absolute (g)	2.68	2.59	2.58	2.72	1.88	1.88	2.01	1.97
rel./BW (%)	0.69	0.71	0.71	0.77*	0.79	0.81	0.86*	0.86*
Liver Absolute (g)	16.0	15.5	14.7*	14.3*	10.43	8.83*	9.43*	9.04*
rel./BW (%)	4.1	4.3	4.1	4.0	4.37	3.79*	3.99*	3.95*
Thymus Absolute (g)	0.32	0.32	0.38	0.30	0.27	0.25	0.23	0.21*
rel./BW (%)	0.08	0.09	0.10*	0.09	0.11	0.11	0.10	0.09*
Prostate Absolute (g)	0.69	0.65	0.57*	0.51*				
rel./BW (%)	0.18	0.18	0.16	0.14*				

⊗ Body weights taken at terminal sacrifice
* Statistically significant ($p < 0.05$)

Repeated iv. administration of telmisartan resulted in no significant differences in Cmax or $AUC_{0\text{-}7hr}$ values between days 1 and 28 (Table 3.2.3.2). Dose proportionality was observed between 0.1 and 2 mg/kg; however, a significant deviation from dose proportionality, with a tendency to higher Cmax and AUC values, was observed between 2 and 20 mg/kg. Plasma concentrations at all doses reflect a high exposure to parent drug in the species tested.

TABLE 3.2.3.2
MEAN PEAK PLASMA CONCENTRATIONS AND AUCs OF TELMISARTAN IN A 4-WEEK INTRAVENOUS TOXICITY STUDY IN RATS

Dose		N	Cmax (µg/ml)				AUC0-7h (µg·h/ml)			
			Male		Female		Male		Female	
(mg/kg)	Day	m/f	Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD
0.1	1	3/3	0.10	0.00	0.09	0.01	0.12	0.01	0.10	0.03
2.0	1	3/3	1.68	0.33	1.60	0.15	2.51	0.44	2.97	0.52
20.0	1	3/3	90.20	4.37	87.90	12.80	114.60	7.43	91.10	7.89
0.1	28	3/3	0.07	0.01	0.07	0.00	0.15	0.02	0.15	0.03
2.0	28	3/3	1.89	0.35	1.93	0.12	3.07	0.39	3.22	0.49
20.0	28	3/3	91.10	5.47	89.90	4.02	123.30	16.20	93.30	13.70

In summary, the 4 weeks administration of telmisartan resulted in mild increases in heart rate, changes in organ weights, an influence on hematopoiesis and kidney function, and gastric mucosal alterations. According to the sponsor, the NOAEL was 0.1 mg/kg; however, this dose decreased both absolute and relative weight of liver by 15% in females.

3.2.4. Thirteen-Week Oral Toxicity Study in Rats (Study #15R, Report #U93-0362) Vol. 33

This GLP study was conducted by

between May 12 and August 10, 1992.

Male and female albino rats were approximately 68 days of age and weighed 279-357 gm (males) or 189-240 gm (females) at the start of the study. Telmisartan (batch #8210040) was administered once daily for 13 weeks at doses of 2, 4, 8 or 32/500 mg/kg by oral gavage. The high dose group initially received 32 mg/kg; on day 8 the dose was increased to 500 mg/kg for the remainder of the study. The control group received the vehicle. Each group consisted of 10 male and 10 female rats. The high dose and control groups contained an additional 10 males and 10 females for a six week recovery phase without dosing. In addition, three satellite animals per dose per sex per group (except control) were used for drug plasma concentration determinations performed before dosing and 1, 2, 4, 7 and 24 hr post-dosing on day 1 and during week 13. According to the report, the high dose of 32 mg/kg was selected based on results of the earlier 2- and 4-week oral toxicity studies. The no observed adverse effect level was lower than 10 mg/kg in the 4-week study, as gastric erosions and renal changes were noted at this dose. On day 8 of the 13-week experiment the high dose was increased to 500 mg/kg to evoke overt clinical and morphological signs of toxicity, especially in males, due to gastric lesions. Furthermore, this higher dose was expected to reveal any non-pharmacologically mediated toxic effects of the test substance. The mid-high and mid-doses of 8 and 4 mg/kg, respectively, were selected to define the threshold for gastric mucosal injury and other pharmacologically-mediated effects. The low dose of 2 mg/kg/day, which is two times the pharmacologically active dose in the renal hypertensive rat and 6 times the pharmacologically active dose in rat angiotensin II pressor response models, was expected to produce no toxic effects.

All animals were observed twice daily during the administration period. The body weight and food and water intake of each animal was determined once a week before and during the dosing period. ECGs were done on 5 animals per sex per group pretest (weeks -2 or -3) and before dosing and 2 and 5 hr after dosing during weeks 5 and 13, and for control and high dose animals, also during the last week of the recovery phase. Indirect systolic blood pressure measurements were done on 3 animals of each sex in the control, 8 and 500 mg/kg groups at the same time points. Hematology and clinical chemistry parameters were examined from blood samples collected in week -2 and in weeks 7 and 12 of the study. The recovery animals were also tested in the 18th week of the study. Urinalysis was performed in study weeks 5 (males) and 6 (females) and also in weeks 12 (males) and 13 (females) and 18 (recovery). Plasma renin activity and aldosterone levels were measured during the last week of dosing. At the end of the administration period and recovery period, all animals were subjected to a complete necropsy that included weighing of selected organs (Table 3.2.4.1). A complete histopathological evaluation was performed on all animals from the control, 8 and 500 mg/kg/day groups. Target organs and tissues showing macroscopical changes from animals in the 2 and 4 mg/kg/day dose groups and recovery group animals also were examined microscopically.

TABLE 3.2.4.1.
TISSUES/ORGANS SAMPLED FOR HISTOPATHOLOGICAL EXAMINATION

Accessory glands	Kidneys*	
Adrenals*	Lachrymal glands	Sublingual salivary glands
Aorta	Liver*	Sciatic nerve, peripheral
Bone marrow	Lungs*	Skeletal muscle
Brain*	Lymph nodes -mesenteric	Skin
Cecum	-neck region	Spinal cord
Colon	Macroscopical lesions	Spleen*
Duodenum	Mammary glands	Sternum
Epididymides	Ovaries*	Stomach
Esophagus	Pancreas	Testes*
Eyes with optic nerves	Parotid salivary glands	Thymus*
Femur	Pituitary*	Thyroid*/parathyroid glands
Heart*	Prostate	Tongue
Ileum	Rectum	Trachea
Jejunum	Seminal vesicles	Urinary bladder
	Submandibular salivary glands	Uterus

* organ weighed

Results

Four high dose animals died or were taken out of the experiment. One male rat was found dead on day 27; two females were sacrificed moribund on days 46 or 64 because of poor clinical condition due to misgavage. Another male was taken out of the experiment on day 95 "due to technical error". The high dose male that died on day 27 had multiple black discolorations of the gastric mucosa, moderate to marked gastric and cecal ulcers and erosions. Drug-related clinical signs were limited to piloerection in the high dose group animals. Ophthalmoscopic examinations revealed dilated retinal vessels in some high dose animals, consistent with the pharmacological activity of the test substance. The body weight gain of rats of the high dose group was significantly less than control (11.2% less for males, 5.4% less for females) during the dosing and recovery periods. Food consumption of high dose males and females was reduced during most of the treatment period, but was comparable to control during most of the recovery period. A dose-dependent significant increase in water consumption (up to 67.7% above concurrent control) was evident in males given 8 or 500 mg/kg, but not in females. Water consumption returned to normal by week 4 of the recovery phase.

Systolic blood pressure was dose-dependently and significantly reduced in weeks 5 and 13 in the 8 and 500 mg/kg dose groups (Table 3.2.4.2). This hypotensive effect persisted 24 hr after dosing. In week 5, no further reduction in b.p. was noted 2 and 5 hr after dosing; in week 13, however, systolic pressure was further reduced after administration of 500 mg/kg. Blood pressure returned to the normal range during the recovery period. No relevant changes in heart rate or ECG occurred.

TABLE 3.2.4.2.

13-WEEK ORAL TOXICITY STUDY IN RATS: HEART RATE AND SYSTOLIC BLOOD PRESSURE

Week	Dose (mg/kg)	Time*	Heart Rate (mean BPM)		Arterial Blood Pressure (Mean mm Hg)		Change in BP (%)⊕
			Mean	(± SD)	Mean	(± SD)	
-2/-3	0	NA	500.5	(12.9)	135.5	(6.0)	
	2		482.3	(14.0)	not recorded		
	4		501.4	(18.8)	not recorded		
	8		511.1	(13.3)	136.4	(5.0)	
	500		491.3	(11.5)	134.1	(4.5)	
5	0	0	495.1	(16.2)	131.5	(4.9)	-3.0
		2	483.2	(14.0)	139.1§	(4.4)	+5.8
		5	467.9	(18.2)	127.9	(9.0)	-2.7
	2	0	504.4	(8.9)	not recorded		
		2	471.0	(13.3)			
		5	494.9	(10.2)			
	4	0	473.2	(12.1)	not recorded		
		2	471.6	(15.3)			
		5	483.6	(14.1)			
	8	0	461.7	(12.8)	104.1§	(3.9)	-23.7
		2	484.8	(17.4)	111.4	(3.8)	+7.0
		5	479.4	(20.0)	109.5	(8.0)	+5.2
	500	0	491.4	(17.8)	83.3§	(4.9)	-37.9
		2	487.6	(20.3)	82.9	(3.1)	-0.5
		5	514.7	(19.4)	69.9	(8.6)	-16.1
13	0	0	481.7	(9.8)	144.1	(7.0)	+6.3
		2	506.9	(9.2)	136.9	(3.6)	-5.0
		5	509.5	(7.6)	125.3	(6.6)	-13.0
	2	0	506.1	(6.0)	not recorded		
		2	509.5	(7.2)			
		5	503.8	(6.1)			
	4	0	490.9	(11.6)	not recorded		
		2	507.5	(10.5)			
		5	500.6	(10.1)			
	8	0	506.2	(13.1)	98.1§	(4.3)	-28.1
		2	515.0	(11.7)	90.4	(4.4)	-7.8
		5	522.9	(9.8)	92.4	(7.5)	-5.8
	500	0	515.6	(19.3)	88.8§	(4.6)	-33.8
		2	521.9	(12.6)	73.2#	(4.8)	-17.6
		5	507.4	(14.3)	74.1#	(4.1)	-16.6
19	0	NA	506.4	(7.7)	134.1	(4.6)	-1.0
	500	NA	506.4	(9.7)	123.7	(5.6)	-7.8

* in hours after administration of drug

⊕ % changes in systolic BP at time 0 and during week 19 are as compared to pretest values. All other % changes are compared to predosing measurements taken on the same day

§ Statistically significant ($p \leq 0.05$) compared to pretest value

\# Statistically significant ($p \leq 0.05$) compared to predosing value on the same day

As compared to the controls, a mild but significant reduction in hemoglobin, erythrocyte count, hematocrit and thromboplastin time was noted in the animals of the high dose group in weeks 7 and 12. Also at the high dose, WBC counts and absolute numbers of neutrophils and lymphocytes in males at week 7 and absolute neutrophil counts in females at week 12 were

significantly increased. All these findings were reversible by week 18. Biochemical changes suggested compound-related effects on the liver and kidneys. Total bilirubin in both sexes given 500 mg/kg and total cholesterol in high dose males also were increased, while total glycerol was decreased in both sexes at this dose. A small increase in alkaline phosphatase was noted for male animals at 500 mg/kg and females at 4 or 8 mg/kg. Blood urea nitrogen of both sexes given 8 or 500 mg/kg and creatinine of high dose animals were increased significantly ($P < 0.01$). In both sexes given 8 or 500 mg/kg and in males given 4 mg/kg, serum potassium levels were slightly elevated; serum magnesium showed a slight increase in high dose males. All these changes were reversible. Plasma renin activity was increased in animals given 2 to 8 mg/kg, but was comparable to control activity in the 500 mg/kg group. Aldosterone levels were decreased in all drug-treated groups, particularly at the high dose. The average urine volume was reversibly decreased and density increased in animals of both sexes given 500 mg/kg. In contrast, urine volume of the animals in the lower three dose groups showed a tendency to increase.

At the 13 week sacrifice, absolute and/or relative decreases in weight were noted for hearts of males and females given 8 or 500 mg/kg/day, thymuses of males at all doses, and livers of high dose males. A trend to decrease in heart weight was noted in females dosed with 2 and 4 mg/kg. Since thymic weights were not strictly dose-dependent, the sponsor considers the decrease toxicologically meaningful only at the high dose. At the 500 mg/kg dose, relative and/or absolute spleen weights were increased in females and adrenal weights were increased in animals of both sexes. Organ weights did not differ from concurrent control when high dose animals were allowed a 6-week recovery period. The details are given in table 3.2.4.3.

TABLE 3.2.4.3.

EFFECT OF TELMISARTAN ON ORGAN WEIGHTS IN RATS TREATED FOR 13 WEEKS

Results expressed as % change in group mean absolute and relative organ weights relative to control. Only statistically significant differences ($p < 0.05$) are given.

Dose (mg/kg/day)		2		4		8		500	
Sex		M	F	M	F	M	F	M	F
Terminal Sacrifice									
Body weight								-9.6	-5.7
Heart	Absolute						-11.9	-20.2	-13.9
	Relative					-9.0	-11.7	-11.6	-9.6
Adrenals	Absolute							+30.3	
	Relative							+44.8	+12.4
Spleen	Absolute								+14.0
	Relative					-13.8			+20.2
Thymus	Absolute	-19.8		-14.2		-11.2		-36.6	
	Relative	-20.7		-15.5		-12.1		-29.3	
Liver	Absolute							-17.2	
	Relative							-8.3	
Recovery Group									
Body weight									-6.7
Heart	Absolute								
	Relative								+8.1
Adrenals	Absolute								+9.9
	Relative								

The principal drug-related macroscopic findings were erosions and ulcers of the gastric mucosa, generally visible as focal red-black discolorations in animals given 500 mg/kg. The main drug-related histopathological changes were in the stomach and kidneys of animals given 8 or 500 mg/kg. Microscopic findings in the stomach are summarized in table 3.2.4.4. Males were more affected than females, with all high dose animals showing evidence of gastric mucosal damage. A gastric ulcer with accompanying submucosal/mucosal inflammation was observed in one 500 mg/kg female, while an additional two high dose females had inflammation consistent with mucosal injury. Healing lesions characterized by submucosal/mucosal fibrosis and/or mild submucosal/mucosal inflammation were observed in 8/9 males and 3/10 females sacrificed in week 19. No evidence of prior mucosal damage was detected in the remaining recovery animals.

TABLE 3.2.4.4.
13-WEEK ORAL TOXICITY STUDY IN RATS: GASTRIC MUCOSAL LESIONS

Histopathological Finding	Dose (mg/kg) Term Sac., Moribund Sac., Found Dead										6 Week Recovery			
	0		2		4		8		500		0		500	
	M	F	M	F	M	F	M	F	M	F	M	F	M	F
No. Animals/Group	10	10	10	10	10	10	10	10	11§	10	10	10	9§	10
Stomach														
Number examined	10	10	9	10	10	10	9	10	11	10	10	10	9	10
No. section submitted	0	0	1	0	0	0	1	0	0	0	0	0	0	0
No. significant findings	10	10	8	10	10	10	8	10	0	7	10	10	1	7
Erosions only	0	0	0	0	0	0	1	0	0	0	0	0	0	0
Ulcers (with or w/o erosions)	0	0	1‡	0	0	0	0	0	7	1	0	0	0	0
Submucosal/mucosal inflam.#														
Mild	0	0	0	0	0	0	1	0	4	2	0	0	4	3
Moderate	0	0	0	0	0	0	0	0	6	1	0	0	0	0
Marked	0	0	0	0	0	0	0	0	1	0	0	0	0	0
Submucosal/mucosal fibrosis	0	0	0	0	0	0	0	0	0	0	0	0	8	3
Total with mucosal injury⊗	0	0	1‡	0	0	0	1	0	11	3	0	0	8	3

‡ Male animal 110 which received 500 mg/kg on days 87 to 91 of the study
§ Male animal 415 (high dose) assigned to the recovery group was sacrificed at Week 13 and is included with the terminal sacrifice group
# Minimal submucosal/mucosal inflammation occurred in both control and drug-treated groups and was not considered indicative of mucosal injury
⊗ Includes animals with active or healing mucosal/submucosal lesions

Drug-related histopathology in the kidney was confined to the juxtaglomerular apparatus and associated afferent arterioles and interlobular arteries of animals given 8 or 500 mg/kg (Table 3.2.4.5.). The findings (juxtaglomerular apparatus hypertrophy, increased renin granules and increased vacuolation) were more pronounced in males than in females and showed, according to the sponsor, partial reversibility at the high dose following the 6-week recovery period. No drug-related degenerative renal tubular changes were detected. Incidence and severity of basophilic tubular change, indicative of spontaneous or induced degeneration (atrophy) or a regenerative response to tubular injury, were similar in all groups.

TABLE 3.2.4.5
13-WEEK ORAL TOXICITY STUDY IN RATS: RENAL PATHOLOGY

Histopathological Finding	Dose Group (mg/kg) Term Sac., Moribund Sac., Found Dead										6-Week Recovery			
	0		2		4		8		500		0		500	
	M	F	M	F	M	F	M	F	M	F	M	F	M	F
No. Animals/Group	10	10	10	10	10	10	10	10	11§	10	10	10	9§	10
KIDNEY														
Number examined	10	10	9	10	10	10	10	10	11	10	10	10	9	10
Tubules normal	2	1	2	2	8	1	1	0	2	1	1	3	1	0
Basophilic tubules														
Minimal	8	9	7ø	7	2	9	9	9	9	7	9	7	8	9
Mild	0	0	0	1	0	0	0	1	0	2	0	0	0	1
No sign. JGA changes	10	10	8	10	10	10	0	0	0	0	10	10	0	0
Increased JGA granules	0	0	1ø	0	0	0	10	10	11	10	0	0	9	0
Increased JGA vacuolation	0	0	1ø	0	0	0	10	10	11	10	0	0	9	10
JGA hypertrophy														
Minimal	0	0	0	0	0	0	0	7	0	0	0	0	1	4
Mild	0	0	0	0	0	0	10	3	1	6	0	0	8	6
Moderate	0	0	1ø	0	0	0	0	0	10	4	0	0	0	0

ø Includes male animal 110 which received 500 mg/kg on days 87 to 91 of the study

§ Male animal 415 originally assigned to the high dose recovery group was sacrificed after 13 weeks of dosing and is included with the terminal sacrifice animals

Liver pathology was noted in high dose animals only and consisted of a subtle decrease in size of centrilobular hepatocytes with a corresponding slight increase in basophilia, relative to control livers (similar in appearance to inanition-associated centrilobular atrophy). Microscopic changes correlated with a mild decrease in liver weight in these animals. These findings may have resulted from a reduction of blood flow as a result of hypotension, and, as such, may be attributable to exaggerated pharmacological activity of the test substance at the high dose.

Other histopathological findings noted in drug-treated animals and attributed to stress included bilateral hypertrophy of the zona fasciculata of the adrenal cortex in five males given 500 mg/kg and minimal to mild cortical lymphoid depletion of the thymus in three high dose males, including the animal that died during the study. The adrenal cortical hypertrophy correlated with increased absolute and relative adrenal weights in high dose males at the 13 week sacrifice and appeared to be reversible. No histopathological abnormalities were detected in females. According to the sponsor, lymphoid depletion of the thymus in high dose males most likely caused the thymic weight decrease in these animals at sacrifice. Similar findings were not detected in males given doses of 2 to 8 mg/kg, despite the minor absolute and relative decreases in thymus weight noted for these groups. Extramedullary hematopoiesis in some high dose females was found to correspond to the increased relative and absolute spleen weights in this group at terminal sacrifice. No microscopic abnormalities were associated with the reduced heart weights of animals given 8 or 500 mg/kg/day.

Mean peak plasma concentrations and AUCs are shown in table 3.2.4.6. Mean AUC and Cmax were dose-proportional in the dose range of 2 to 32 mg/kg on day 1, whereas values for the 500

mg/kg dose were distinctly higher than expected. There were no significant differences between sexes or with repeated dosing (day 1 *vs.* week 13).

TABLE 3.2.4.6.
13-WEEK ORAL TOXICITY STUDY IN RATS: TOXICOKINETICS

Dose (mg/kg)	Time	N m/f	Cmax (µg/ml)				AUC0-24h (µg·h/ml)			
			Male		Female		Male		Female	
	Day		Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD
2	1	3/3	0.06	0.01	0.070	0.01	0.67	0.11	0.95	0.18
4	1	3/3	0.16	0.06	0.103	0.02	1.78	0.42	0.97	0.10
8	1	3/3	0.23	0.19	0.174	0.01	2.50	1.20	2.18	0.25
32‡	1	3/3	0.78	0.19	3.030	2.86	11.10	3.60	16.60	10.00
500	1	3/3	83.10	24.00	78.500	32.00	863.00	300.00	660.00	450.00
	Week									
2	13	3/3	0.08	0.03	0.10	0.06	1.09	0.45	1.35	0.27
4	13	3/3	0.22	0.12	0.29	0.09	2.76	1.30	2.09	0.50
8	13	3/3	0.42	0.10	0.55	0.13	5.04	1.50	5.22	0.47
500	13	3/3	81.10	22.00	119.00	65.00	796.00	440.00	1410.00	1300.00

‡ Plasma concentrations for 32 mg/kg dose measured on day 1 only.

In summary, 13-weeks of repeated daily doses of telmisartan resulted in clinical laboratory and histopathological changes (partly reversible) that were qualitatively similar to those observed in a 4-week study performed in the same strain of rat. The high dose, 500 mg/kg/day, was lethal to one animal. The principal target organ effects (occurring in the stomach and kidney) were considered to result from exaggerated pharmacological activity of the test substance. Treatment with telmisartan was associated with pronounced and persistent decreases in blood pressure. Males were more sensitive than females at comparable doses, plasma concentrations and AUC's. The sponsor's claim of 4 and 8 mg/kg/day NOAELs for males and females, respectively, is incorrect. In females, it could be 2 mg/kg/day and in males it could be still lower, since decreases in thymus weight were observed at all dose levels. It should be noted that peak plasma concentrations and $AUCs_{0\text{-}24\ hr}$ in males and females at 2 mg/kg/day (measured in week 13) were in the range of 31-82 ng/ml and 52-58 ng/ml, and 818-1605 ng.h/ml and 1093-1627 ng.h/ml, respectively. For reference, a single clinical dose of 20 mg telmisartan in normal healthy volunteers achieved a mean Cmax of 34 ng/ml and mean AUC of 402 ng.h/ml on the 7th day of treatment (values are means for parent drug combined for males and females) (study #502.124).

3.2.5. 26-Week Oral Toxicity Study of Telmisartan in Rats
(Study #65R and 08S, Report #U94-2130) Vol. 45-49

This GLP study was conducted by[redacted]. It was conducted in two parts, #65R (January 20, 1993 to August 19, 1993) and #80S (August 4, 1993 to February 15, 1994) due to toxicity seen at the initial low-dose of 4 mg/kg/day.

Animals: Male and female albino rats
Age at study start: Study #65R, 48 days; Study #08S, 55 days
Weight at study start: Study #65R, Males: 198.8-216.8 gm, Females: 152.6-175.4 gm;
Study #08S, Males: 221.8-256.3 gm, Females: 169.1-197.8 gm.

The test substance (batch 8230231) was administered as a suspension in 0.5% Natrosol® 250HX (hydroxyethylcellulose) at a volume of 10 ml/kg body weight. The control animals received the same quantity of 0.5% Natrosol® 250HX. Telmisartan was given each day in the morning, using a tuberculin syringe and stomach tube, for 26 weeks, 7 days a week. The study design was as follows.

Study #	Substance	Dose	Main study		Toxicokinetic study	
			Males	Females	Males	Females
65R	Natrosol	10 ml/kg/d	20	20	5	5
65R	Telmisartan	4.0 mg/kg/d	20	20	5	5
65R	Telmisartan	50.0 mg/kg/d	20	20	5	5
65R	Telmisartan	500.0 mg/kg/d	20	20	5	5
08S	Natrosol	10 ml/kg/d	20	20	5	5
08S	Telmisartan	0.1 mg/kg/d	20	20	5	5
08S	Telmisartan	1.0 mg/kg/d	20	20	5	5

The doses were selected on the basis of 4-week (see section 3.2.3) and 13-week oral administration studies in which doses of 4 or more mg/kg/day caused dose-related changes in the glandular stomach, the liver and the kidneys. Evidence of erosions and ulcers of the mucosa of the glandular stomach was found at all dosage levels. Since the no observed adverse effect level in the 13-week study was 4 mg/kg/day, the same was chosen as a low dose for the 26-week study, #65R. But during an early evaluation of study #65R, the sponsor noted decreases in body weight gain and food consumption in males receiving 4 mg/kg/day. This led the sponsor to add additional low doses, 0.1 and 1 mg/kg/day (study #08S), so as to reach a no observed adverse effect level or threshold for adverse findings in study #65R.

Observations and Measurements

Clinical Observations: at least twice daily on working days (once on non-working days).
Body Weight, and Water and Food Consumption: weekly.
Heart Rate, ECG (n=10) and Blood Pressure (n=6, tail cuff method): week -1 (prestudy) and study weeks 5, 13, 25 at 0 and 2 and 5 hr after administration.
Ophthalmoscopic Examination (study #65R only): week -2 and during study weeks 12 and 25.
Hematology and Clinical Chemistry: weeks 13 and 26 of the study.

Urinalysis: study #65R, weeks 14 and 25; study #08S, weeks 13 and 25.
Feces Examined for Occult Blood: weeks 9 and 23 of the study.
Plasma Renin and Aldosterone Levels: at the end of the last dose administration period blood samples were collected from 4-5 animals/ex/group.
Plasma Telmisartan: study days 1 (study #65R/#08S) at 0, 1, 2, 4, 7 and 24 hr postdose; 85 (only study #08S) at 0 and 2 hr postdose; 176 (only study #08S), and 180 (only study #65R) at 1, 2, 4, 7 and 24 hr postdose.
Post-Mortem Examinations: A complete necropsy was performed on all animals except those used for toxicokinetics, and all macroscopic changes were recorded. The following organs or tissues were collected from all animals on study. Of the organs listed below, both eyes were fixed in Davidson solution; all other tissues were fixed in 10% neutral buffered formalin. Representative sections of all tissues collected at necropsy from all animals of the control and high dose groups and from one low dose (4 mg/kg/day) male that died prematurely, were processed for microscopic examination. For the remaining groups, target organs (kidneys, stomach and duodenum, and liver) and tissues showing macroscopical alterations were microscopically examined. Spleens of females receiving 50 mg/kg/day were also examined.

Accessory glands (males)
Adrenals*
Aorta
Bone marrow
Brain*
Cecum
Colon
Duodenum
Epididymides
Esophagus
Eyes with optic nerves
Femur
Heart*
Ileum
Jejunum
Kidneys*
Lachrymal glands
Liver*
Lungs*
Lymph nodes -mesenteric
-neck region
Macroscopical lesions
Mammary glands
Ovaries*
Pancreas
Parotid salivary glands
Pituitary*
Prostate
Rectum
Seminal vesicles
Submandibular salivary glands
Sublingual salivary glands
Sciatic nerve, peripheral
Skeletal muscle
Skin
Spinal cord
Spleen*
Sternum
Stomach
Testes*
Thymus*
Thyroid*/parathyroid glands
Tongue
Trachea
Urinary bladder
Uterus

* organ weighed

Results

A total of 12 rats (including two animals from the toxicokinetics study) died or were sacrificed for humane reasons during the study (Table 3.2.5.1). At the high dose, 5 males and 4 females died and one male was sacrificed moribund. Gastrointestinal injury was considered the cause of death in these high dose animals. In addition to GI changes, some of them showed drug-induced hypertrophy, hyperplasia and/or vacuolation of the juxtaglomerular apparatus, bilateral proximal tubular degeneration of the kidney associated with hyaline casts, bilateral segmental degenerative changes in the semniferous tubules of the testes, bilateral hypertrophy of the zona fasciculata of the adrenal gland, acinar atrophy of the salivary gland, and/or thymic lymphoid depletion. There were three other losses, a moribund sacrifice of a male at 4 mg/kg/day and the deaths of two females (satellite animals) one each at 50 and 500 mg/kg/day (Table 3.2.5.1).

TABLE 3.2.5.1
EFFECT OF TELMISARTAN ON SURVIVAL IN RATS, 26 WEEKS ORAL ADMINISTRATION

Dose (mg/kg/day)	# of deaths M	F	Study Wk	Day	Probable cause of death
4	1		22	150	Killed moribund. Had food-filled, dilated esophagus consistent with impaction and bilateral hydrocephalus
50		1	26	180	Satellite animal. Not examined
500	1		2	12	Dead; gastric and intestinal ulcer/erosion/inflammation; hypertrophy, hyperplasia of JGA of the kidney; mild splenic congestion.
	1		3	19	Dead; gastric and intestinal ulcer/erosion/inflammation; bilateral, segmental degenerative changes in the semniferous tubules of the testes.
		1	8	53	Satellite animal. Not examined
		1	9	62	Dead; gastric and intestinal ulcer/erosion/inflammation; bilateral hypertrophy of the zona fasciculata of the adrenal gland.
	1		10	69	Sacrificed moribund; gastric and intestinal ulcer/erosion/inflammation; bilateral, segmental degenerative changes in the semniferous tubules of the testes; bilateral proximal tubular degeneration of the kidney, associated with hyaline casts; bilateral hypertrophy of the zona fasciculata of the adrenal gland; acinar atrophy of the salivary gland and thymic lymphoid depletion.
		1	10	70	Dead; gastric ulcer/erosion; bilateral hypertrophy of the zona fasciculata of the adrenal gland; and thymic lymphoid depletion.
	1		11	76	Sacrificed moribund; gastric and intestinal ulcer/erosion/inflammation; bilateral, segmental degenerative changes in the seminiferous tubules of the testes; bilateral hypertrophy of the zona fasciculata of the adrenal gland; acinar atrophy of the salivary gland and thymic lymphoid depletion.
		1	16	112	Dead; gastric and intestinal ulcer/erosion/inflammation; bilateral hypertrophy of the zona fasciculata of the adrenal gland; and thymic lymphoid depletion.
		1	24	166	Dead; gastric ulcer/erosion; congenital unilateral vascular malformation in the lateral ventricle of the brain.
	1		26	181	Dead; gastric ulcer/erosion; bilateral hypertrophy of the zona fasciculata of the adrenal gland.

Body weight gain was dose-dependently and significantly reduced in males at 4 or more mg/kg/day in all weeks of treatment. In females, body weight was significantly reduced at 4 mg/kg for several weeks (starting with week 16) and at 500 mg/kg/day in all study weeks. Although 50 mg/kg/day females weighed the same as 4 mg/kg/day females, the former group did not differ significantly from control (Table 3.2.5.2, Fig 3.2.5.1).

TABLE 3.2.5.2

EFFECT OF TELMISARTAN ON BODY WEIGHT AND BODY WEIGHT GAIN IN 26 WEEK RAT STUDY

Dose, mg/kg/day		Study #08S			Study #65R			
		Control	0.1	1	Control	4	50	500
Absolute body weight (gm)	M	531.0	530.7	511.5	565.4	503.4*	468.6*	413.8*
	F	284.9	290.0	282.6	297.0	283.8*	285.4	274.2*
Deviation of body wt. relative to control (%)	M	-	0	-4	-	-11	-17	-27
	F	-	+2	-1	-	-4	-4	-8
Body weight gain (%)¶	M	66	66	61	72	55	45	27
	F	33	33	31	39	36	36	30

¶ : percent increase relative to start of administration

* : decrease statistically significant ($p < 0.05$)

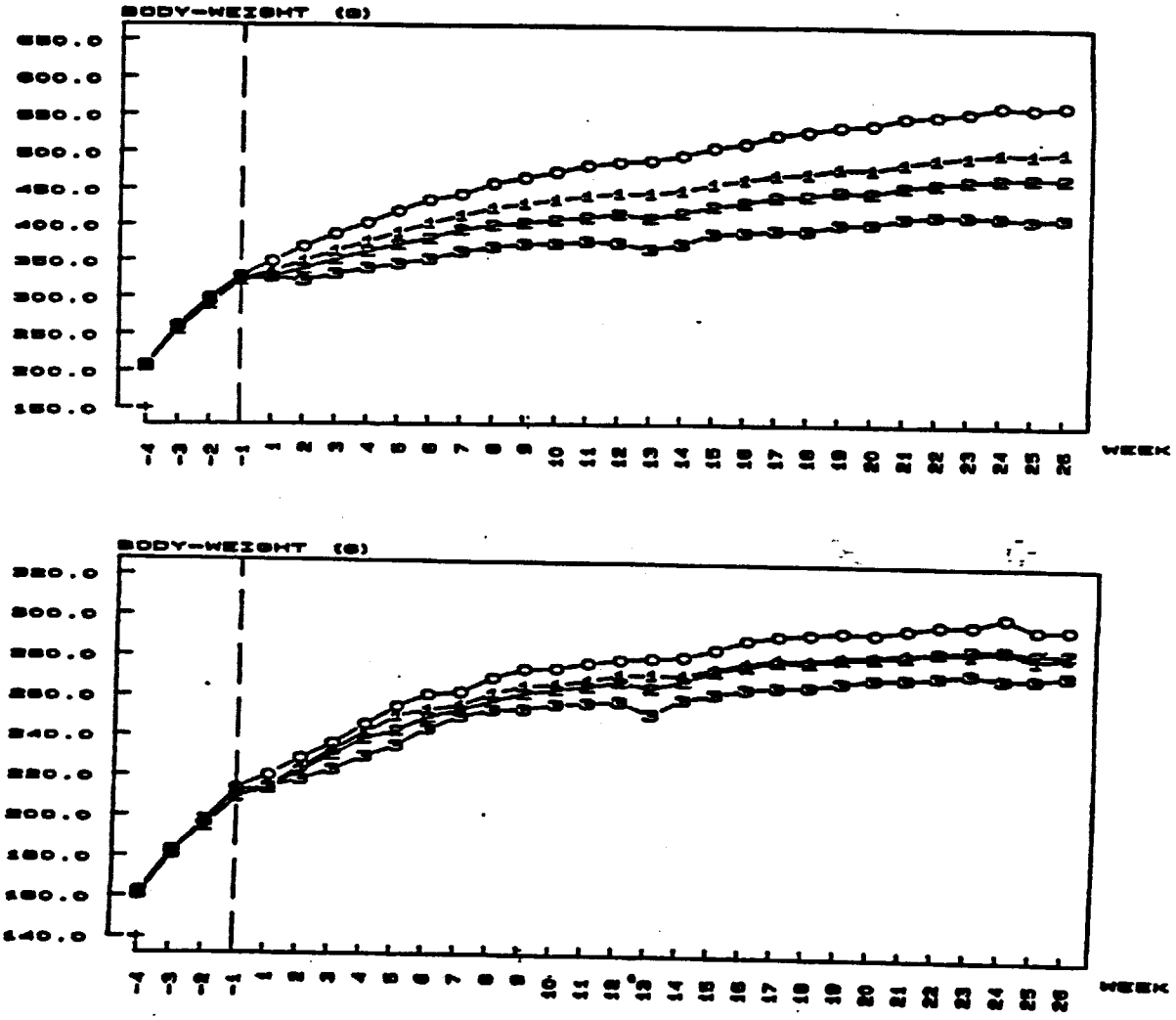

Fig. 3.2.5.1.: 26-week toxicity of telmisartan. Group mean body weight changes in male (top) and female (bottom) rats. 0: Control, 1: 4 mg/kg/day, 2: 50 mg/kg/day, 3: 500 mg/kg/day.

Food consumption for males was significantly reduced (6 to 13% relative to control) at 4 or more mg/kg/day in almost all study weeks and was generally dose-dependent until week 19. For females, a significant decrease in food consumption was noted at the high dose in weeks 1 to 9 with a maximum deviation of 16% in study week 3. By study week 14, the high dose values approximated the control values. Water consumption for males receiving 1 and 4 mg/kg/day was comparable to control. A dose-dependent increase in water intake was noted for males receiving 50 or more mg/kg/day throughout the dosing period. No clear dose response relationship was noted for females. At 1 and 4 mg/kg/day, water consumption by females was increased in almost all weeks, whereas it was below control consumption at 50 mg/kg/day. At 500 mg/kg/day, water consumption was significantly increased in study weeks 3 through 20.

Changes in systolic blood pressure were noted at 1 (week 25 only) or more mg/kg/day, with a dose-dependent decrease observed at doses of 4 or more mg/kg/day. Pre-administration values in these groups were markedly reduced, suggesting that the effect lasted for more than 24 hours. No biologically relevant changes in heart rate or ECG were noted. Ophthalmoscopic examinations revealed dilated blood vessels in the fundus at the 500 mg/kg/day dose level.

Hematological findings included dose-dependent decreases in erythrocytic parameters (RBC, hemoglobin, hematocrit) in rats receiving 50 or more mg/kg/day (Table 3.2.5.3). Also observed were slightly reduced mean corpuscular hemoglobin (MC\H), mean corpuscular volume (MCV) and mean corpuscular hemoglobin concentration (MCHC) values in these high dosage groups. At study week 13, platelet counts were significantly reduced (dose-independent) in males receiving 4 or more mg/kg/day and at study weeks 13 and 26 thromboplastin time was decreased ($p<0.05$, dose-dependent) in both sexes receiving 50 or more mg/kg/day (Table 3.2.5.3). There were no bone marrow changes.

TABLE 3.2.5.3.
TELMISARTAN: NOTABLE HEMATOLOGY FINDINGS IN RATS

Parameter	Week	Sex	Dose (mg/kg/day)						
			Study #08S			Study #65R			
			Ctl	0.1	1	Ctl	4	50	500
Erythrocytes ($x10^6/mm^3$)	w 13	M	8.07	8.02	7.95	8.38	8.28	7.34$^{\$}$	6.17$^{\$}$
		F	7.69	7.57	7.51	7.70	7.47*	6.83$^{\$}$	6.24$^{\$}$
	w 26	M	8.39	8.33	8.40	8.07	8.00	6.85$^{\$}$	6.21$^{\$}$
		F	7.98	7.79*	7.72$^{\$}$	7.56	7.26$^{\$}$	6.82$^{\$}$	6.71$^{\$}$
Hemoglobin (g/100 ml)	w 13	M	15.8	15.5	15.7	16.3	16.0	14.3$^{\$}$	11.3$^{\$}$
		F	15.4	15.3	14.9$^{\$}$	15.4	14.8$^{\$}$	13.6$^{\$}$	11.8$^{\$}$
	w 26	M	15.7	15.6	15.7	15.9	15.7	13.5$^{\$}$	11.6$^{\$}$
		F	15.5	15.2*	14.8$^{\$}$	15.2	14.7*	13.7$^{\$}$	12.9$^{\$}$
Hematocrit (vol. %)	w 13	M	47.7	46.8	47.3	48.6	48.1	43.3$^{\$}$	34.6$^{\$}$
		F	46.1	45.7	44.9$^{\$}$	46.0	44.6$^{\$}$	41.1$^{\$}$	35.6$^{\$}$
	w 26	M	47.0	47.2	47.4	48.0	47.6	41.0$^{\$}$	35.9$^{\$}$
		F	46.6	45.6$^{\$}$	44.7$^{\$}$	45.4	44.4*	41.5$^{\$}$	39.4$^{\$}$
MCH (pg)	w 13	M	19.6	19.4	19.8	19.5	19.3	19.5	18.4$^{\$}$
		F	20.1	20.3	19.9	20.0	19.8	20.0	18.9$^{\$}$
	w 26	M	18.7	18.7	18.7	19.7	19.6	19.7	18.7$^{\$}$
		F	19.4	19.6	19.2	20.1	20.2	20.1	19.3$^{\$}$
MCHC (g/100 ml)	w 13	M	33.1	33.2	33.2	33.6	33.2*	33.0$^{\$}$	32.7$^{\$}$
		F	33.5	33.6	33.3	33.4	33.2	33.2	33.1
	w 26	M	33.5	33.0*	33.1*	33.2	33.0	32.9	32.3$^{\$}$
		F	33.3	33.4	33.1	33.4	33.1	33.1	32.9
MCV (μm^3)	w 13	M	59.1	58.4	59.5	58.1	58.1	59.1	56.3*
		F	60.0	60.4	59.8	59.7	59.7	60.2	57.0$^{\$}$
	w 26	M	56.0	56.6	56.5	59.5	59.5	59.8	58.1
		F	58.5	58.5	57.9	60.2	61.1	60.8	58.8*
Thrombocytes ($1000/mm^3$)	w 13	M	655	617	615	740	648$^{\$}$	653$^{\$}$	610$^{\$}$
		F	701	665	668	703	688	698	694
	w 26	M	592	576	602	721	652	667	720
		F	639	657	638	737	737	755	763
Thromboplastin time (sec)	w 1	M	21.0	21.2	20.8	20.9	20.8	20.1*	19.2$^{\$}$
		F	18.5	18.6	19.0	19.7	19.5	18.8*	17.9$^{\$}$
	w 26	M	19.5	19.5	19.9	20.5	20.7	19.5*	19.3*
		F	18.4	18.5	18.3	18.9	18.8	18.5	17.9$^{\$}$

Significant when compared with control: *: $p < 0.05$; $^{\$}$: < 0.01

Biochemical findings included slight but dose-dependent increases ($P > 0.05$) in alkaline phosphatase in males receiving 4 or more mg/kg/day and significant increases in females receiving 4 and 500 mg/kg/day, relative to controls. Higher than control levels of total bilirubin ($P < 0.01$) were observed in high dose rats in both weeks of measurement. Dose-dependent increases ($P < 0.05$-0.01) in blood urea nitrogen were noted in male and female animals of the 4 or more mg/kg/day groups. Though increases in creatinine values over control were dose-dependent at 50 and 500 mg/kg/day, the data was only significant for the high dose group. Total cholesterol was increased ($p < 0.01$) in male animals dosed at 50 or more mg/kg/day; an increase was noted in high dose females ($p < 0.01$) in week 13 only. Total protein and total glycerol were

dose-dependently reduced ($p < 0.05$-0.01) in both male and female rats receiving 4 or more mg/kg/day (Table 3.2.5.4). The apparent effects of telmisartan on total glycerol and cholesterol indicate an influence of the drug on lipid metabolism. A non-dose-dependent increase ($p < 0.01$) in potassium and magnesium relative to controls was noted for both sexes dosed at 50 or more mg/kg/day.

TABLE 3.2.5.4
EFFECT OF TELMISARTAN ON BLOOD CHEMISTRY DURING 26 WEEK TOXICITY STUDY IN RATS
(Results expressed as group mean values)

Parameter	Week	Sex	Dose (mg/kg/day)						
			Study #08 S			Study #65 R			
			Ctl	0.1	1	Ctl	4	50	500
Alkaline Phosphatase (U/l)	w 13	M	190	194	187	201	211	224	232
		F	140	135	128	137	169**	144	187**
	w 26	M	172	172	169	190	189	198	211
		F	127	122	120	130	153*	125	148*
Total bilirubin (µmol/l)	w 13	M	1.1	1.4*	1.1	1.2	1.4	1.3	3.3**
		F	1.2	1.2	0.6**	1.0	1.1	1.3	2.2**
	w 26	M	1.2	1.5*	1.0	1.3	1.4	1.3	2.4**
		F	0.9	1.3**	0.9	1.4	1.4	1.3	2.2**
Total cholesterol (mmol/l)	w 13	M	1.54	1.54	1.52	1.75	1.66	2.04**	2.08**
		F	1.57	1.56	1.54	1.83	1.97	2.01	2.21**
	w 26	M	1.74	1.75	1.77	1.75	1.70	2.12**	1.98**
		F	1.95	2.01	2.04	1.96	2.08	2.15	2.16
Total glycerol (mmol/l)	w 13	M	4.88	4.64	4.00	4.39	3.35**	2.59**	1.72**
		F	3.12	2.77	1.99*	3.53	2.91	2.64	1.92**
	w 26	M	5.44	5.40	4.47	4.79	3.63**	2.62**	1.58**
		F	3.29	3.82	3.55	4.94	4.02*	3.19**	2.23**
Total protein (g/l)	w 13	M	61.5	61.2	61.2	65.0	63.4*	60.9**	54.0**
		F	62.9	62.7	61.3	64.5	62.4*	60.4**	58.1**
	w 26	M	64.6	64.0	65.0	65.4	64.4	60.1**	57.3**
		F	65.8	66.8	66.0	68.4	65.8**	64.8**	60.7**
Urea (mmol/l)	w 13	M	7.11	7.55	7.63	7.63	10.70	21.23**	29.00**
		F	7.83	7.96	8.11	8.93	10.03	13.08**	24.83**
	w 26	M	7.70	7.50	7.35	6.62	8.72**	21.10**	25.61**
		F	8.91	8.60	9.11	7.83	8.99	11.19**	14.88**
Creatinine (µmol/l)	w 13	M	42.5	43.1	43.5	46.6	47.7	50.8	59.8**
		F	44.6	44.6	43.6	46.7	48.2	49.5	58.9**
	w 26	M	47.4	45.4	46.2	45.3	46.6	52.4**	58.3**
		F	47.4	46.1	46.7	46.7	47.4	49.6	50.7*
Potassium (mmol/l)	w 13	M	4.33	4.26	4.56*	4.24	4.62*	6.17**	5.87**
		F	3.91	3.83	4.37**	4.09	4.39*	4.82**	5.55**
	w 26	M	4.39	4.29	4.31	4.37	4.65*	6.40**	5.91**
		F	4.30	4.08	4.27	4.22	4.47	4.96**	4.99**
Magnesium (µmol/l)	w 13	M	724	733	718	711	721	922**	936**
		F	785	803	810*	762	788	852**	975**
	w 26	M	703	706	711	706	731	990**	909**
		F	791	791	804	771	777	831**	826**

Significant when compared with control: * $p \leq 0.05$ and ** $p \leq 0.01$

Urinalyses showed a dose-dependent decrease ($p < 0.05$ at 50 or more mg/kg/day) in urine volume relative to controls at 4 or more mg/kg/day. A few high dose animals showed positive findings of occult blood in feces which could be due to the loss of blood *via* erosions/ulcers of the glandular stomach mucosa.

At the 26 week sacrifice, a dose-dependent absolute decrease (5.4 to 29%) in heart weight was noted for males receiving 0.1 or more mg/kg/day. Absolute reductions in heart weight for females compared to control were 10, 13 and 10.5% at 4, 50 and 500 mg/kg/day, respectively (Table 3.2.5.5). A significant but non-dose-related increase in relative kidney weight was observed for males (8.6 to 26%) at 4 or more mg/kg/day and for females (2.7 to 6.5%) at 1.0 or more mg/kg/day. Absolute liver weights for males given 4 or more mg/kg/day were lower (9 to 25%) than control. Increased spleen (36% relative in males, 25% absolute in females) and decreased thymus (47% absolute in males, 20% absolute in females) and gonad (20% absolute for testes, 30% absolute for ovaries) weights were noted for both sexes at 500 mg/kg/day (Table 3.2.5.5).

TABLE 3.2.5.5
SIGNIFICANT ORGAN WEIGHT CHANGES IN MALES AFTER 26 WEEKS OF DOSING

Organ / Tissue	Dose (mg/kg)							
	08 S			65 R				
	0	0.1	1.0	0	4.0	50	500	
Body Weight (grams)	526.7	526.2	511.7	562.3	505.6*	472.0*	411.1*	↓
HEART absolute (grams)	1.437	1.359*	1.298*	1.447	1.213*	1.071*	1.031*	↓
relative (% BW)	0.274	0.259*	0.254*	0.258	0.240*	0.227*	0.252	↓
relative (% BrW)	0.668	0.634	0.611*	0.648	0.552*	0.490*	0.489*	↓
KIDNEY absolute (grams)	3.261	3.180	3.088	3.409	3.332	3.105	3.116	
relative (% BW)	0.621	0.608	0.606	0.607	0.660*	0.659*	0.764*	↑
relative (% BrW)	1.515	1.486	1.455	1.526	1.519	1.420*	1.478	↓
LIVER absolute (grams)	20.462	20.098	19.326	20.818	18.920*	17.334*	15.649*	↓
relative (% BW)	3.881	3.833	3.776	3.692	3.736	3.673	3.812	
relative (% BrW)	9.500	9.393	9.104	9.316	8.625*	7.936*	7.416*	↓
THYMUS absolute (grams)	0.168	0.164	0.157	0.158	0.137*	0.134*	0.083*	↓
relative (% BW)	0.032	0.031	0.031	0.028	0.027	0.028	0.020*	↓
relative (% BrW)	0.078	0.077	0.074	0.071	0.063	0.061	0.040*	↓
SPLEEN absolute (grams)	0.863	0.868	0.820	0.859	0.782	0.709	0.844	
relative (% BW)	0.164	0.166	0.160	0.152	0.155	0.150	0.207*	↑
relative (% BrW)	0.401	0.406	0.386	0.384	0.356	0.325	0.400	
TESTES absolute (grams)	3.839	3.617	3.664	3.896	3.671	3.690	3.105*	↓
relative (% BW)	0.736	0.694	0.722	0.696	0.729	0.784*	0.753*	↑
relative (% BrW)	1.784	1.691	1.726	1.744	1.671	1.689	1.469*	↓

* Statistically significant ($p<5\%$) when compared with concurrent control

TABLE 3.2.5.5 (CONTINUED)
SIGNIFICANT ORGAN WEIGHT CHANGES IN FEMALES AFTER 26 WEEKS OF DOSING

ORGAN / TISSUE	DOSE (MG/KG)							
	08 S			65 R				
	0	0.1	1.0	0	4.0	50	500	
Body Weight (grams)	285.3	288.8	282.7	298.9	283.8*	288.8	275.4*	↓
HEART absolute (grams)	0.934	0.957	0.947	0.974	0.877*	0.847*	0.872*	↓
relative (% BW)	0.328	0.332	0.335	0.326	0.309*	0.294*	0.317	↓
relative (% BrW)	0.475	0.477	0.480	0.474	0.429*	0.431*	0.444	↓
KIDNEY absolute (grams)	2.253	2.342	2.415*	2.334	2.401	2.397	2.487*	↑
relative (% BW)	0.792	0.811	0.856*	0.781	0.848	0.832*	0.904*	↑
relative (% BrW)	1.144	1.166	1.225*	1.135	1.175	1.217*	1.266*	↑
LIVER absolute (grams)	11.135	11.633	11.533	11.760	11.628	11.433	11.189	
relative (% BW)	3.904	4.016	4.078	3.937	4.100	3.954	4.073	
relative (% BrW)	5.653	5.792	5.842	5.722	5.691	5.806	5.703	
THYMUS absolute (grams)	0.128	0.134	0.132	0.134	0.131	0.127	0.107*	↓
relative (% BW)	0.045	0.046	0.047	0.045	0.046	0.044	0.039	
relative (% BrW)	0.065	0.067	0.067	0.065	0.064	0.064	0.055*	↓
SPLEEN absolute (grams)	0.612	0.636	0.584	0.591	0.530	0.581	0.736	↑
relative (% BW)	0.215	0.221	0.207	0.199	0.187	0.201	0.269	↑
relative (% BrW)	0.311	0.317	0.296	0.288	0.259	0.295	0.375	↑
OVARY absolute (mg)	99.37	102.04	95.87	109.98	102.97	95.36*	77.23*	↓
relative (% BW)	34.822	35.368	33.675	36.687	36.406	33.112	27.845*	↓
relative (% BrW)	50.401	50.860	48.580	53.450	50.576	48.076	38.925*	↓

* Statistically significant ($p<5\%$) when compared with concurrent control

There were no drug-related gross pathological findings in rats given 0.1 or 1 mg/kg/day. At higher doses, animals dying or killed moribund, and survivors to term had macroscopical evidence of gastric mucosal injury (discoloration, erosions, crateform lesions or thickening of the gastric wall). Incidence was 1, 8 and 15 males and 0, 2 and 6 females in the 4, 50 and 500 mg/kg/day groups, respectively. The following findings were noted only at the highest dose: intestinal changes of edema or wall thickening, particularly of the cecum (3 males and 1 female) or watery/discolored content (1 male and 3 females), evidence of anemia (3 males), thymic atrophy (2 males), decreased testicular/epididymal size (3 males) and adrenal enlargement (1 male and 1 female) (also see Table 3.2.5.1, Mortality).

GI and kidney were considered the principal organs of toxicity. At 1 mg/kg, JGA hypertrophy was noted in 19/20 males and 8/20 females, and JGA vacuolation in 2 males, were the only drug-related findings. At doses of 4 or more mg/kg/day, the principal drug-related microscopic findings were JGA hypertrophy, hyperplasia and vacuolation (Table 3.2.5.6) and gastrointestinal ulcer, erosion, inflammation and fibrosis (Table 3.2.5.7). Other findings in surviving animals included increased extramedullary hematopoiesis of the spleen in high dose males (9 of 15 *versus* 3 of 20 controls), increased incidence of splenic congestion in high dose females (6 of 16 *versus* no controls), and thymic lymphoid depletion in high dose animals of both sexes (5 of 15 males and 4 of 16 females compared to 1 animal of each sex in the concurrent control group). An increased incidence of bilateral, segmental atrophy of the seminiferous tubules of the testes was

observed in 10 (including 3 rats sacrificed moribund or prematurely) of 20 high dose males and was accompanied by reduced spermatogenesis of the testes and/or oligospermia of the epididymides in 4 surviving animals. This was considered by the sponsor to have resulted from the reduced weight of the testes. There were no notable changes in prostate, seminal vesicles or accessory glands in this dose group. In females, ovarian atrophy was observed in 6 of 16 surviving high dose females and 2 of 20 concurrent controls, possibly indicative of an effect on the reproductive system similar to that observed in males. Once again, the sponsor attributes the effect to the reduced absolute and relative weights of the ovaries. No drug-related effects on the remainder of the female reproductive tract were detected.

TABLE 3.2.5.6
INCIDENCE OF RENAL PATHOLOGY IN RATS AFTER 26 WEEKS OF DOSING

Study Number	**08 S**		**65 R**		**08 S**		**08 S**		**65 R**		**65 R**		**65 R**	
Dose Level (mg/kg/day)	**0**	**0**	**0**	**0**	**0.1**	**0.1**	**1.0**	**1.0**	**4.0**	**4.0**	**50**	**50**	**500**	**500**
Sex	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**
# Animals per Group	**20**	**20**	**20**	**20**	**20**	**20**	**20**	**20**	**20**	**20**	**20**	**20**	**20**	**20**
# Organs/ Tissues Examined	**20**	**20**	**20**	**20**	**20**	**20**	**20**	**20**	**20**	**20**	**20**	**20**	**20**	**20**
Number of Animals														
Tubular/Interstitial Changes														
No Tubular/Interstit. Changes	7	0	2	0	3	0	1	0	0	0	0	0	1	0
Nephrocalcinosis	1	20	0	20	0	20	0	20	0	20	0	20	0	20
Slight	*1*	*6*	*0*	*9*	*0*	*6*	*0*	*1*	*0*	*13*	*0*	*10*	*0*	*8*
Mild	*0*	*9*	*0*	*8*	*0*	*10*	*0*	*7*	*0*	*6*	*0*	*7*	*0*	*10*
Moderate	*0*	*5*	*0*	*3*	*0*	*4*	*0*	*12*	*0*	*1*	*0*	*3*	*0*	*2*
Tubular Atrophy	9	11	14	8	9	12	14	14	8	18	20	18	18	20
Slight	*9*	*11*	*14*	*8*	*9*	*12*	*14*	*14*	*8*	*18*	*20*	*18*	*16*	*20*
Mild	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*2*	*0*
Tubular Basophilia	3	3	1	0	2	0	2	0	0	0	4	0	9	2
Slight	*3*	*3*	*1*	*0*	*2*	*0*	*2*	*0*	*0*	*0*	*4*	*0*	*8*	*2*
Mild	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*1*	*0*
Interstitial Inflammation	13	10	18	8	17	9	17	13	17	15	20	20	18	20
Slight	*13*	*10*	*18*	*8*	*17*	*9*	*17*	*13*	*17*	*15*	*20*	*20*	*16*	*19*
Mild	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*2*	*1*
JGA Changes														
No JGA Changes	20	20	20	20	20	20	1	12	0	0	0	0	1*	0
JGA Hypertrophy	0	0	0	0	0	0	19	8	20	20	20	20	19	20
Slight	*0*	*0*	*0*	*0*	*0*	*0*	*19*	*8*	*0*	*7*	*0*	*0*	*0*	*0*
Mild	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*20*	*13*	*1*	*6*	*1*	*3*
Moderate	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*19*	*14*	*18*	*17*
JGA Hyperplasia	0	0	0	0	0	0	0	0	20	13	20	20	19	20
Slight	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*3*	*6*	*1*	*3*	*0*	*0*
Mild	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*17*	*7*	*19*	*8*	*1*	*7*
Moderate	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*9*	*18*	*13*
JGA Vacuolation	0	0	0	0	0	0	2	0	20	19	20	20	19	20
Slight	*0*	*0*	*0*	*0*	*0*	*0*	*2*	*0*	*19*	*15*	*3*	*4*	*2*	*4*
Mild	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*1*	*4*	*17*	*16*	*17*	*16*

* Animal # 305, found dead on day 12 had no JGA changes

TABLE 3.2.5.7
INCIDENCE OF GASTROINTESTINAL LESIONS IN RATS AFTER 26 WEEKS OF DOSING

Study Number	08 S		65 R		08 S		08 S		65 R		65 R		65 R	
Dosage (mg/kg/day)	0		0		0.1		1.0		4.0		50		500	
Sex	M	F	M	F	M	F	M	F	M	F	M	F	M	F
# Animals per Group	20	20	20	20	20	20	20	20	20	20	20	20	20	20
# Organs / Tissues Examined	20	19	20	20	20	20	20	20	19	20	20	20	20	20
Number of Animals														
No Relevant GI Findings	8	12	10	19	16	16	18	16	13	12	0	1	0	0
Nonglandular Stomach														
Mucosal Erosion	0	0	0	0	0	0	0	0	0	1	0	0	0	0
Glandular Stomach														
Submuc./Mucosal Inflammation														
Slight	5	5	8	1	4	4	2	4	3	4	1	2	0	1
Mild	7	2	2	0	0	0	0	0	2	3	3	12	2	4
Moderate	0	0	0	0	0	0	0	0	0	0	16	4	16	15
Marked	0	0	0	0	0	0	0	0	0	0	0	0	1	0
Submucosal / Mucosal Fibrosis	0	0	0	0	0	0	0	0	1	0	18	19	16	18
Mucosal Erosion	2	0	1	0	0	0	0	0	1	0	7	2	11	7
Mucosal Ulcer	0	0	0	0	0	0	0	0	0	1	10	3	13	9
Intestinal Tract**														
Duodenal Injury	0	1	0	0	0	0	0	0	0	0	0	0	1	1*
Cecal Injury	0	0	0	0	0	0	0	0	0	0	0	0	4*	4*
Colonic Injury	0	0	0	0	0	0	0	0	0	0	0	0	4	1
Total: Drug-induced GI Injury§	0	0	0	0	0	0	0	0	2	1	18*	19*	20*	20*

* Animal no. 356 had lesions in both duodenum and cecum; animals no. 303 and 359 had lesions in colon and cecum. All animals with intestinal lesions also had stomach lesions.

** The duodenal, cecal, and colonic injuries comprise the following findings: inflammation, edema, erosion, ulcer. Each animal with one or more of these findings is listed.

§ **Lesions in the stomach considered drug-induced were erosions, ulcers, inflammation moderate or greater in severity and fibrosis, slight to marked. In the intestine, ulcers, erosions and inflammation (any grade) combined with edema were judged to be drug-induced.** (No animals with slight or mild submuc./mucosal inflammation are included because these changes were also observed in control animals and consequently not considered to be drug-related. Gastric mucosal erosions in 3 control males, one at the junction of glandular and nonglandular mucosa, one in the antrum and one in the fundus, were considered incidental.)

No significant differences in telmisartan plasma concentrations were noted between males and females. Telmisartan plasma concentrations were not consistent with dose proportionality for either males or females. Repeated dosing resulted in accumulation yielding an increase in Cmax and $AUC_{0\text{-}24h}$ in week 26 (6 to 18-fold increase from week 1 to week 26) (Table 3.2.5.8). The accumulation of telmisartan might be a result of two effects which are additive: (a) the normal accumulation due to a half-life of elimination >5 hr, and (b) the non-linear kinetics.

TABLE 3.2.5.8
PHARMACOKINETIC PARAMETERS OF TELMISARTAN IN RATS DURING THE 26 WEEK TOXICITY STUDY

Sampling time	Dose mg/kg/day	tmax (h) MEAN		Cmax (µg/ml)				AUC 0-24h (µg.h/ml)			
				Male		female		male		female	
		male	female	MEAN ± SEM		MEAN ± SEM		MEAN ± SEM		MEAN ± SEM	
Week 1 (Day 1)	0.1	17.2	24.0	0.0059	0.001	0.0188	0.001	0.112	0.021	0.206	0.013
	1.0	6.4	2.4	0.0386	0.003	0.0340	0.006	0.571	0.030	0.454	0.056
	4.0	2.8	1.8	0.1480	0.012	0.1840	0.015	1.630	0.084	1.770	0.092
	50.0	1.6	1.0	3.4900	0.760	3.2100	0.950	19.900	3.520	16.300	3.810
	500.0	6.0	6.0	43.3000	6.060	106.0000	27.700	301.000	119.000	604.000	160.000
Week 26 (Day 176/180)	0.1	4.2	1.6	0.0062	0.001	0.0106	0.001	0.105	0.017	0.095	0.011
	1.0	2.4	1.4	0.0595	0.007	0.0802	0.009	0.706	0.038	0.698	0.081
	4.0	1.8	2.0	3.3200	1.310	3.5900	0.816	30.900	6.790	38.600	7.230
	50.0	2.2	2.4	21.8000	3.030	29.5000	12.100	123.000	57.200	124.000	35.800
	500.0	8.2	1.0	76.8000	11.100	173.0000	18.800	1030.000	84.800	1570.000	378.000

In summary, 26-weeks oral administration of telmisartan to normotensive rats resulted in dose-dependent hypotension at doses of 1 to 500 mg/kg/day, lasting for >24 hr. Excluding satellite animals, 5 males and 4 females from the high dose group died or were sacrificed in moribund condition, and the deaths were attributed to gastric mucosal injury. Body weight gain and food consumption were reduced for both sexes at 4 or more mg/kg/day. Dose-dependent decreases in erythrocytic parameters, protein and total glycerol were observed in rats receiving 4 or more mg/kg/day. Microscopic examination revealed hyperplasia/hypertrophy of the JGA apparatus at doses of 1 or more mg/kg/day, and this may have triggered higher plasma urea and creatinine concentrations. At doses of 50 or more mg/kg/day, gastrointestinal ulceration, erosion, inflammation and fibrosis were observed. Thymic lymphoid depletion and gonadal atrophy in high dose animals, with corresponding organ weight decreases, were considered secondary to reduced body weight and stress associated with the GI effects of the test substance. The toxicokinetic parameters revealed an increase in telmisartan plasma levels (AUC and Cmax) between beginning and end of drug administration, suggesting accumulation of drug in the range of 6 to 18-fold. A no observed adverse effect level was not defined in this study.

3.2.6. One Month Oral Toxicity Study in Dogs (Study #89O, Report #U92-0333) Vol. 20-22

This GLP study was conducted by

between October 11 and February 3, 1992.

Male and female dogs Beagle and Beak) were approximately 7-14 months of age and weighed 10.9-14.1 kg (males) or 9.3-14.7 kg (females) at the start of the study. Telmisartan (batch #8110110) was administered once daily for 28 days at doses of 10, 40, 60 or 160 mg/kg by oral gavage. The control group received the vehicle. Each group consisted of 3 male and 3 female dogs. The two high dose groups contained an additional 3 males and 3 females for a seven weeks recovery phase without dosing. The doses were selected on the basis of a two week oral dose-range finding study in which dosages of 125 or more mg/kg/day caused increased plasma levels of urea nitrogen, creatinine and magnesium suggestive of renal functional impairment. Additionally, a reduction in red blood cell parameters was noted at 250 or more mg/kg/day, and sporadic emesis occurred at 500 mg/kg/day. White particles in the feces as well as a marked variability of the substance plasma concentrations showed that the substance absorption was incomplete in this dose range. In view of these findings, 160 mg/kg was chosen as the high dose level for the one month study. The low dose of 10 mg/kg/day was approximately 30 times the pharmacologically active oral dose of 0.3 mg/kg in dogs given angiotensin II and was expected to elicit no adverse effects. The mid dose of 40 mg/kg was selected to investigate the dose-response for toxic effects. (Due to a technical error, the high dose group which should have received 160 mg/kg, actually received 60 mg/kg during the initial weeks of the study. An additional 160 mg/kg dose group was added to the study once the error was recognized).

All animals were observed twice daily during the administration period. The body weight and food consumption of each animal was determined once a week before and during the dosing period. Electrocardiograms and direct arterial blood pressure (via a cannulated femoral artery) were recorded in conscious state pretest, and before dosing and 2 and 4 hours postdosing during weeks 1 and 4, and during week 9 in recovery groups. Hematology and clinical chemistry parameters were examined from blood samples collected pretest and in the 4th week of the study. The recovery animals were also tested in the 9th week of the study. Urinalysis was performed pretest and in study weeks 4 and 9 (recovery). Plasma concentrations of telmisartan were measured in dogs dosed with 10, 40 and 160 mg/kg/day before dosing on day 1 and 1, 2, 3, 5, 7, 15 and 24 hr post-dosing on days 1, 15 and 25. At the end of the drug administration period and recovery period, all animals were subjected to a complete necropsy that included weighing of selected organs and complete histopathological evaluation.

Results

There were no deaths in the study. Emesis was observed in drug-treated animals and one vehicle control on single days during the dosing phase of the study, but frequency was not strictly dose-related. Females given 160 mg/kg had markedly reduced body weight and food consumption relative to control females. Significant reductions in blood pressure and slight increases in heart rate were observed at all doses. During week four, 47 to 51% reductions in diastolic blood pressures and 34 to 39% reductions in systolic pressures were recorded in high dose group

animals (Table 3.2.6.1). No tolerance was noted with repeated dosing. Reversibility of cardiovascular effects was demonstrated for the two high dose groups during the recovery period. No arrhythmias were noted.

TABLE 3.2.6.1.
HEART RATE AND BLOOD PRESSURE IN DOGS GIVEN TELMISARTAN ORALLY FOR 4 WEEKS

Week	Dose (mg/kg)	Time*	n	Heart Rate (BPM)		Arterial Blood Pressure (BP) (mmHg)				Change in BP (%)⊗	
						Systolic		Diastolic		Syst.	Diast.
				Mean	(±SEM)	Mean	(±SEM)	Mean	(±SEM)		
-1	0	NA	6	108.0	(12.6)	182.0	(8.7)	92.0	(6.0)	NA	
	10		6	115.5	(9.1)	188.0	(6.1)	98.2	(4.2)		
	40		6	123.0	(16.7)	189.5	(6.6)	103.0	(6.7)		
	60		6	127.0	(18.9)	192.5	(3.9)	104.2	(3.4)		
	160		6	117.0	(10.2)	189.2	(4.0)	101.7	(4.3)		
1	0	0	6	114.0	(12.8)	173.0	(4.7)	79.5	(3.2)	-4.9	-13.6
		2	6	116.5	(11.0)	174.7	(7.0)	85.2	(5.4)	+1.0	+7.2
	10	0	6	145.7	(12.4)	148.2	(7.9)	67.2	(5.3)	-21.2	-31.6
		2	6	130.7	(10.8)	149.0	(6.6)	71.8	(5.7)	+0.5	+6.8
	40	0	6	136.3	(11.9)	143.8	(8.6)	63.7	(8.2)	-24.1	-38.2
		2	6	127.3	(7.7)	143.5	(11.9)	69.7	(9.4)	-0.2	+9.4
	60	0	6	137.3	(15.9)	157.3	(5.3)	74.2	(8.9)	-18.3	-28.8
		2	6	137.0	(13.9)	156.0	(5.4)	75.5	(5.1)	-0.8	+1.8
	160	0	6	134.5	(11.9)	175.8	(13.2)	92.7	(10.5)	-7.1	-8.8
		2		137.0	(8.1)	175.0	(16.3)	93.7	(9.8)	-0.5	+1.1
4	0	0	6	128.7	(8.3)	171.3	(4.4)	89.3	(5.0)	-5.9	-2.9
		2	6	116.0	(10.2)	172.8	(3.6)	89.8	(2.2)	+0.9	+0.6
	10	0	6	139.2	(12.0)	116.3	(8.2)	47.8	(3.2)	-38.1	-51.3
		2	6	126.7	(9.9)	128.8	(10.0)	56.7	(5.5)	+10.7	+18.6
	40	0	6	129.7	(12.7)	120.7	(6.8)	51.2	(4.9)	-36.3	-50.3
		2	6	124.7	(11.6)	129.7	(7.1)	57.8	(5.4)	+7.5	+12.9
	60	0	6	127.3	(14.2)	126.3	(2.3)	55.0	(2.4)	-34.4	-47.2
		2	6	141.8	(11.7)	134.7	(7.4)	63.0	(4.9)	+6.7	+14.5
	160	0	6	150.7	(11.8)	116.0	(3.2)	49.7	(2.2)	-38.7	-51.1
		2	6	143.7	(12.0)	119.3	(3.8)	49.0	(3.2)	+2.8	-1.4
9	60	NA	6	125.0	(9.3)	176.2	(4.8)	96.2	(3.8)	-8.5	-7.7
	160		6	119.0	(11.5)	179.7	(10.1)	98.3	(6.7)	-5.0	-3.3

* In hours after administration of drug

⊗ Mean BPs at time 0 h (predosing) and during the recovery phase (Week 9) are compared to pretest (Week -1) values.
All other comparisons are to predosing values on that particular study day.

Slight reductions in RBC count, hematocrit and hemoglobin and a slight increase in erythrocyte sedimentation rate were noted for individual animals in all drug-treated groups. Bone marrow evaluation revealed a slight decrease in red cell precursors in the high dose group. In most of the animals, at all dose levels, a significant increase in the urea nitrogen, as compared to the initial value was documented. This effect was dose-dependent and reversible. In many males and

females of all treated groups, magnesium demonstrated a tendency to increase in comparison to the initial values. No changes in urinalyses were noted.

Mild dose-dependent increases in mean absolute and relative liver weight (up to 25%) were observed in males at doses of 60 and 160 mg/kg. At necropsy, gastric and/or duodenal mucosal erosions and/or ulcers were observed at doses of 40 mg/kg and higher. Histopathological evaluation confirmed pyloric and/or proximal duodenal ulcers and/or erosions in these groups of animals (see Table 3.2.6.2). Severity of mucosal lesions was not dose-dependent. It seems male dogs were slightly more susceptible than females in that the lesions developed at 40 or more mg/kg in males but only at 60 mg/kg and higher dosages in females. Similar lesions were not observed in animals sacrificed after the six week recovery period, demonstrating reversibility.

TABLE 3.2.6.2
INCIDENCE OF GASTRIC AND DUODENAL MUCOSAL EROSIONS AND ULCERS IN DOGS GIVEN TELMISARTAN ORALLY FOR FOUR WEEKS

Dose, mg/kg/day	Animal No.	Stomach	Duodenum
40	201 M	isolated erosions	
60	301 M		mucosal redness
	303 M	isolated erosions	
	353 F		1 ulcus
	355 F	mucosal redness	
160	401 M		1 ulcus
	402 M	1 erosion	1 erosion
	403 M	1 erosion	
	451 F		1 erosion
	452 F		2 erosions

As in rats, multifocal hyperplasia of the granular epithelioid cells of the juxtaglomerular apparatus with prominent cell granularity was observed in the kidneys of all drug-treated animals. Incidence of the affected renal corpuscles and intensity of the hyperplasia and granularity were dose-dependent. These changes were apparently reversible as only one high dose male showed (slight) JGA cell hyperplasia, and without granularity, after drug withdrawal. A variety of renal tubular findings (single cell necrosis, mild degeneration, mild lipofuchscinosis and moderate epithelial vacuolation of the pars recta) were reported for individual high dose animals sacrificed at term; these changes were not observed in animals sacrificed after the recovery period.

Telmisartan was slowly and in some instances biphasically absorbed, with a median Tmax of 7-15 hr (range 1-24 hr). Plasma levels increased with increasing dose and tended to be higher in females than males (Table 3.2.6.3). However, due to the small sample size (n=3/dose/sex) and high interindividual variabilities in plasma concentrations, there were no statistically significant differences in Cmax or AUC between males and females. It may be noted that peak concentrations reached at the low dose of 10 mg/kg/day, the "minimally toxic dose" in both rat

and dog, were 400 to 500 ng/ml, comparable to those attained in the 4-week rat study at the same dose (mean 300 to 400 ng/ml). No evidence of accumulation was found.

TABLE 3.2.6.3
4-WEEK ORAL TOXICITY STUDY IN DOGS: TOXICOKINETICS

Dose (mg/kg)	Day	n (group) m/f	Cmax (µg/ml)				AUC (µg·h/ml)			
			males		females		males		females	
			Mean	(± SD)	Mean	(± SD)	Mean	(± SD)	Mean	(± SD)
10	1	3/3	0.4	0.1	0.4	0.1	4.7	1.3	5.4	1.3
40	1	3/3	1.7	0.6	3.8	2.0	24.2	9.7	38.2	16.9
160	1	3/3	8.3	3.0	7.8	12.3	97.1	32.7	147.1	141.6
10	25	3/3	0.4	0.1	0.5	0.1	7.0	1.0	7.0	1.0
40	25	3/3	1.7	0.2	5.2	5.4	21.0	5.1	57.2	54.6
160	25	3/3	12.8	11.4	15.8	14.8	170.3	133.8	122.7	104.5

In summary, in addition to the expected pharmacodynamic activity, telmisartan caused slight reductions in some hematological parameters in individual animals of all drug-treated groups. Furthermore, slight increases in urea nitrogen and magnesium were observed in individual animals of the highest dosage group. Morphologically, hyperplasia of the juxtaglomerular apparatus in all drug treated dogs, and gastric and/or duodenal mucosal erosions and/or ulcers were observed in dogs receiving 40 mg/kg and higher. Plasma concentrations of telmisartan at a dosage of 10 mg/kg/day in dog were comparable to those attained in the 4-week rat study at the same dose (300 to 400 ng/ml).

3.2.7. One Month Intravenous Toxicity Study in Dogs (Study #08R, Report #U92-0797) Vol. 25-26

This GLP study was conducted by

between April 28 and July 6, 1992.

Male and female beagle dogs were approximately 9-11 months of age and weighed 10.4-13.0 kg (males) or 8.4-12.9 kg (females) at the start of the study. Telmisartan (batch #8110130) was administered iv, once daily for 28 days at doses of 0.5, 5, or 50 mg/kg, at approximately 10 ml/min (1% solution, injection time: 3 sec to 5 min). The control group received the vehicle (5 ml/kg). Each group consisted of 3 male and 3 female dogs. The high dose group (only) contained an additional 3 males and 3 females for a 6-week recovery phase without dosing. Test substance was dissolved in required quantities of 1 N NaOH, 1 N HCl, NaCl and water for injection. The final pH of the solution is not given. The high dose was selected on the basis of a two week iv dose-range finding study in which emesis and defecation occurred at dosages of 40 and 80 mg/kg/day, with salivation and sedation at the higher dose. Increased urea nitrogen, creatinine and renal tubular changes occurred at 40 mg/kg and higher; increased liver function enzymes and Juxtaglomerular apparatus changes were noted at 80 mg/kg. The low dose (0.5 mg/kg/day) chosen for the one month study is approximately 15-50 times the pharmacologically active (reduction of pressor response to angiotensin II) iv dose of 0.01 to 0.03 mg/kg in dogs.

All animals were observed twice daily during the administration period. The body weight and food consumption of each animal was determined a week before and once a week during the dosing period. Electrocardiograms and direct arterial blood pressure (via a cannulated femoral artery) were recorded in the conscious state pretest, and before dosing and 30 min (and 3 hr for ECG only) postdosing during weeks 2 and 4, and during week 10 in the recovery group. Hematology and clinical chemistry parameters were examined from blood samples collected pretest and in the 4th week of the study. The recovery animals were also tested in the 10th week of the study. Urinalysis was performed pretest and in weeks 4 and 10 (recovery). Plasma renin activity and aldosterone levels were determined on day 24. Plasma concentrations of telmisartan were measured before dosing on day 1 and 1, 10 and 30 min and 1, 2, 3, 5, 7 and 24 hr post-dosing on days 1 and 24. At the end of the administration period and recovery period, all animals were subjected to a complete necropsy that included weighing of selected organs and a complete histopathological evaluation.

Results

There were no deaths in the study. Emesis was observed immediately after dosing with increased frequency in high dose animals. A slight, dose-related, decrease in food consumption and loss of body weight was noted for all 4 weeks of measurement for females given 5 ($P > 0.05$) or 50 ($P < 0.05$) mg/kg. The weight gain normalized during the recovery period (Table 3.2.7.1). Dose-dependent decreases in b.p., lasting for 24 hr, were recorded for both sexes at all doses and were more pronounced at week 4 than in week 2. Decreases were reversible for high dose animals at the end of the recovery period. No changes in heart rate and no electrocardiograph abnormalities were evident.

TABLE 3.2.7.1
EFFECT OF TELMISARTAN ON BODY WEIGHT IN FEMALE DOGS: GROUP MEAN VALUES (in Kg)

Dose (mg/kg/day)	Study Weeks								
	-1	1	2	3	4	5	6	7	8
Control	10.5	10.6	10.6	10.8	10.9				
Telmisartan 0.5	11.1	11.0	11.1	11.2	11.2				
Telmisartan 5	8.9	8.8	8.7	8.9	8.8				
Telmisartan 50	11.4	11.2*	11.1*	10.9*	10.9*				
Telmisartan 50 recovery	11.3	11.0*	10.8*	10.8*	10.6*	11.1	11.1	11.1	11.2

*: decrease statistically significant ($p < 0.05$)

Decreases in RBC count, hematocrit and hemoglobin were observed in several animals given 50 mg/kg, as well as one male each in the 0.5 and 5 mg/kg dose groups. Reduced platelet counts also were noted for several high dose animals of both sexes. At the high dose, all females and 1 male had increased SGPT, SGOT and LDH levels. Five of 6 high dose animals, and 2 males and one female in the mid dose group showed moderate increases in BUN. Also, individual high (7 of 12) and mid (2 of 6) dose animals displayed increased creatinine and magnesium. All biochemical changes were reversible. Plasma renin activity was increased at 0.5 and 5 mg/kg, but comparable to control in animals given 50 mg/kg. Both absolute and relative weights of kidneys of males given 5 or 50 mg/kg, livers of high dose animals of both sexes and adrenals of high dose females were elevated in comparison to control. Drug-related microscopic findings were limited to the kidney, where increased granularity of the J-G apparatus was observed in all dogs of the high dose group and in one male given 5 mg/kg/day.

Plasma level determinations of telmisartan in all dose groups revealed (dosage-dependent) systemic exposure to the drug (Table 3.2.7.2). Significant sex differences were not detected and repeated dosing had no effect on plasma concentrations or AUC. At higher doses, deviation from dose proportionality with a tendency to higher than expected AUC (but not C_{max}) was observed.

TABLE 3.2.7.2
4-WEEK INTRAVENOUS ADMINISTRATION STUDY IN DOGS: TOXICOKINETICS

Dose (mg/kg/d)	Day	N m/f	Cmax (µg/ml)				AUC0-24h (µg·h/ml)			
			Male		Female		Male		Female	
			Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD
0.5	1	3/3	6.14	7.23	1.03	0.21	1.34	0.83	0.96	0.18
5.0	1	3/3	33.83	38.9	35.31	17.3	16.17	4.5	16.83	3.3
50.0	1	3/3	189.44	32.0	210.87	55.3	327.49	35.0	362.46	31.9
0.5	24	3/3	2.81	2.95	7.40	3.37	1.49	0.49	2.11	0.66
5.0	24	3/3	18.62	4.2	51.92	30.3	16.43	1.7	21.81	6.8
50.0	24	3/3	214.13	56.7	312.89	44.6	282.05	23.3	338.73	47.5

In summary, repeated daily intravenous doses of telmisartan at levels up to 50 mg/kg/day resulted in only mild manifestation of toxicity in dogs, despite high exposure levels and pronounced pharmacodynamic effects. Clinical laboratory examinations suggested effects on kidney and liver, mainly at the high dose. The NOAEL in this study was 0.5 mg/kg/day.

3.2.8. Thirteen-Week Oral Toxicity Study in Dogs (Study#14R, Report #U93-0361) Vol. 30-32

This GLP study was conducted by

between May 5 and September 14, 1992.

Male and female beagle dogs were approximately 15-21 months of age and weighed 11-14.6 kg (males) or 9.3-13.9 kg (females) at the start of the study. Telmisartan (batch #8210040) was administered once daily for 13 weeks at doses of 5, 10, 20 or 50 mg/kg by oral gavage. The control group received the vehicle. Each group consisted of 3 male and 3 female dogs. The high dose group contained an additional 3 males and 3 females for a six week recovery phase without dosing. The doses were selected based on results of the previous 2- and 4-week oral toxicity studies. The no observed adverse effect level was lower than 10 mg/kg in the 4-week study, as decreases in red cell parameters and increases in urea nitrogen were observed in individual animals at dose of 10 or more mg/kg/day. Evidence of gastric mucosal injury was present at doses of 40 or more mg/kg/day. 50 mg/kg was selected as the high dose for the 13-week study. The low dose of 5 mg/kg, which is 15 times the pharmacologically active dose in the dog, was expected to produce no toxic effects. The 10 and 20 mg/kg doses were expected to define the threshold for toxicity and to elucidate the dose response for toxicity with chronic dosing.

All animals were observed twice daily during the administration period. The body weight and food consumption of each animal was determined a week before and once a week during the dosing period. Electrocardiograms and direct arterial blood pressure were recorded in conscious state pretest, and before dosing and 2 hours postdosing during weeks 6 and 13, and during week 19 in recovery groups. Hematology and clinical chemistry parameters were examined from blood samples collected pretest and in the 6th and 12th weeks of the study. The recovery animals were also tested in the 19th week of the study. Urinalysis was performed in study weeks -2, 6, 12 and 19 (recovery). Plasma renin activity and aldosterone levels were determined in blood samples collected from all animals at the end of the administration period. Plasma concentrations of telmisartan were measured in blood samples collected from all dogs except control and recovery groups before dosing (0 hr) and 1, 2, 3, 5, 7, 15 and 24 hr post-dosing on days 1 and 91. At the end of the administration period and recovery period, all animals were subjected to a complete necropsy that included weighing of selected organs and a complete histopathological evaluation.

Results

There were no deaths in the study. Increased incidence of vomiting was observed in most animals of the 50 mg/kg/day dose group and one animal each given 10 or 20 mg/kg/day (time and frequency of vomiting not given). A white substance, presumably drug, was seen in the feces at 20 and 50 mg/kg/day. Slightly reduced body weight gain was noted only for the males given 20 mg/kg. One animal each in the 10 and 20 mg/kg groups showed reduced food consumption. As in rats, enlarged retinal vessels consistent with vasodilation were observed on ophthalmoscopical examination in several animal of all drug-treated groups. This reflects the pharmacological effect of the test substance.

TABLE 3.2.8.1.
TISSUES/ORGANS SAMPLED FOR HISTOPATHOLOGICAL EXAMINATION

Adrenals*
Aorta
Bone marrow
Brain*
Cecum
Colon
Duodenum
Epididymides
Esophagus
Eyes with optic nerves
Femur
Heart*
Ileum
Jejunum
Kidneys*
Lachrymal glands
Liver*
Lungs*
Lymph nodes -jejunalis, popliteus, cervicalis
Macroscopical lesions
Mammary glands
Ovaries*
Pancreas
Parotid glands
Pituitary*
Prostate
Rectum
Seminal vesicles
Submandibular salivary glands
Sublingual salivary glands
Sciatic nerve, peripheral
Skeletal muscle
Skin
Spinal cord (neck, chest, lumbar)
Spleen*
Sternum
Stomach (cardia, fundus, pylorus)
Testes*
Thymus*
Thyroid*/parathyroid
Tongue
Trachea
Urinary bladder
Uterus

* organ weighed

In all dose groups, diastolic and systolic blood pressures were significantly reduced in weeks 6 and 13. The effect was more pronounced in week 13. After the recovery period, pressures in the high dose group increased, but remained below pre-test levels. Small increases in heart rate were observed in the 20 and 50 mg/kg groups 2 and 5 hr after dosing in week 6 only (Table 3.2.8.2).

In all male animals given 20 and 50 mg/kg, as well as in all females given 10 mg/kg and higher, slight, non-dose-dependent, reversible decreases in hemoglobin, RBC count, and hematocrit, as compared with initial values, was observed. Individual animals receiving 10 mg/kg and higher doses also showed slight, reversible increases in platelet count. BUN was increased in a non-dose dependent manner in one low dose male and in most of the animals given 10 mg/kg or higher, while creatinine also was slightly increased in one female receiving 10 mg/kg and in some animals given 20 or 50 mg/kg. Magnesium increased slightly in most of the animals of the 50 mg/kg dose group, as well as individual animals of the 10 and 20 mg/kg groups. Changes in biochemical parameters and electrolytes were reversible. Plasma renin activity was increased in animals of both sexes given 5 or 10 mg/kg and in females of the 20 mg/kg group. Values for the 20 and 50 mg/kg males and 50 mg/kg females were not significantly different from control. Aldosterone determinations showed an increase in the 10 mg/kg group compared to controls and to the other dose groups, with marked individual variation.

TABLE 3.2.8.2
13-WEEK ORAL TOXICITY STUDY IN DOGS: HEART RATE AND BLOOD PRESSURE

Wk	Dose (mg/kg)	Time (h)	Heart Rate (BPM)		Arterial Blood Pressure (BP) (mm Hg) Diastolic		Systolic		Change in BP (%)[§] Systolic	Change in BP (%)[§] Diastolic
			Mean	(± SEM)	Mean	(± SEM)	Mean	(± SEM)		
-1	0	NA	144.8	(6.8)	118.3	(5.3)	199.7	(11.2)	NA	NA
	5		115.2	(11.6)	116.5	(3.3)	219.7	(3.8)		
	10		112.8	(10.0)	110.8	(4.8)	203.8	(6.9)		
	20		125.3	(6.4)	114.7	(4.9)	207.7	(5.3)		
	50		87.7	(9.7)	112.8	(6.9)	208.0	(11.5)		
6	0	0	146.7	(8.8)	120.2	(5.9)	185.5*	(6.7)	-12.4	+1.6
		2	147.0	(11.9)	114.0	(5.6)	181.1	(6.2)	-2.4	-5.2
		5	151.5	(11.5)						
	5	0	124.3	(15.7)	84.0*	(5.7)	50.2*	(5.4)	-31.6	-27.9
		2	135.5	(13.6)	80.8	(2.4)	146.3	(2.4)	-2.6	-3.8
		5	136.8	(17.0)						
	10	0	125.7	(10.3)	73.5*	(5.7)	130.2*	(7.3)	-36.1	-33.7
		2	124.2	(12.1)	71.3	(53.8)	126.3	(6.4)	-3.0	-3.0
		5	136.0	(14.3)						
	20	0	128.0	(3.4)	82.8*	(10.5)	137.8*	(12.6)	-33.7	-27.8
		2	141.2**	(5.3)	84.2	(9.2)	145.5	(8.9)	+5.6	+1.7
		5	139.8**	(4.7)						
	50	0	115.8*	(7.9)	75.7*	(7.8)	136.5*	(9.7)	-34.4	-32.9
		2	130.5**	(13.0)	69.8	(7.8)	139.2	(3.9)	+2.0	-7.8
		5	121.3	(8.7)						
13	0	0	128.5	(12.0)	100.0*	(5.9)	199.7	(11.2)	-5.7	-15.5
		2	124.3	(12.5)	100.5	(6.3)	191.0	(9.4)	-4.4	+0.5
		5	125.8	(14.1)						
	5	0	128.0	(16.9)	60.3*	(3.5)	136.2*	4.8)	-38.0	-48.2
		2	124.8	(16.5)	67.0**	(2.9)	151.8	(3.7)	+11.5	+11.1
		5	115.5	(16.7)						
	10	0	111.5	(8.4)	70.8*	(4.6)	143.0*	(5.8)	-29.8	-36.1
		2	103.0	(8.3)	69.3	(4.6)	141.2	(7.8)	-1.3	-2.1
		5	103.0	(10.2)						
	20	0	127.2	(11.3)	61.8*	(2.6)	136.5*	(4.1)	-34.3	-46.1
		2	121.2	(5.6)	61.7	(4.3)	151.8	(3.7)	+3.3	-0.2
		5	118.3	(7.2)						
	50	0	95.0	(8.3)	54.7*	(3.7)	141.8*	(7.0)	-31.8	-51.5
		2	105.8	(10.5)	54.8	(3.2)	138.2	(7.4)	-2.5	+0.02
		5	93.7	(5.7)						
19	50	0	81.7	(9.5)	94.5*	(4.7)	187.5*	(7.1)	-9.9	-16.2

[§] BPs at time 0 and during Week 19 are compared to pretest values.
All other comparisons are to predosing measurements taken on the same day
* Statistically significant ($p<0.05$) compared to pretest value
** Statistically significant ($p<0.05$) compared to predosing value on the same day

Organ weights differed from control only at the lower doses and thus were considered not to be of toxicological relevance. As in previous studies, drug-related histopathological changes were mainly restricted to the stomach and kidneys. Lesions in the gastric mucosa, thought to be ulcers

or erosions of minimal grade, were observed at term sacrifice in 2 high dose males. Microscopic examination revealed focal hyperemia and subepithelial edema in one of these high dose animals and focal inflammation with slight epithelial loss in the pyloric region of the other. Drug-induced histopathologic changes in the kidney were confined to the juxtaglomerular apparatus of dogs of all groups. These changes comprised multifocal juxtaglomerular apparatus hypertrophy/hyperplasia and increased vacuolation. The intensity of the alteration was dose-dependent and reached a moderate intensity in the high dose group. JGA changes were partially reversible in the high dose group following the 6-week recovery period. One male each in the 20 and 50 mg/kg dose groups had moderately increased hemosiderin storage in the Kupffer cells and macrophages of the liver.

As with other oral studies, telmisartan was slowly absorbed, and characterized by inter-animal variability and a biphasic concentration profile with a half-life >10 hr. Cmax and $AUC_{0\text{-}24hr}$ increased proportionally with dose and were significantly higher in week 13 compared to day 1. No differences between males and females were apparent (Table 3.2.8.3).

TABLE 3.2.8.3
13-WEEK ORAL TOXICITY STUDY IN DOGS: TOXICOKINETICS

Dose (mg/kg)	Day	N (group) m/f	Cmax (µg/ml)				AUC (µg·h/ml)			
			Male		Female		Male		Female	
			Mean	(± SD)	Mean	(± SD)	Mean	(± SD)	Mean	(± SD)
5	1	3/3	0.18	0.02	0.19	0.04	2.6	0.38	2.2	0.82
10	1	3/3	0.22	0.07	0.30	0.08	3.0	0.81	3.7	0.82
20	1	3/3	0.72	0.35	0.72	0.33	10.1	5.1	9.4	4.6
50	1	3/3	2.60	0.75	1.80	0.59	31.0	12.0	20.0	6.4
5	91	3/3	0.20	0.01	0.28	0.12	3.2	0.31	3.1	1.4
10	91	3/3	0.28	0.08	0.85	0.36	3.9	1.9	9.2	2.0
20	91	3/3	2.00	2.00	1.20	0.76	20.4	18.0	14.4	12.0
50	91	3/3	5.10	3.10	4.00	1.70	51.1	32.0	47.0	28.0

In summary, 13 weeks of oral administration of telmisartan to dogs resulted in side effects known from previous experiments. Reduced RBC parameters and increased BUN, magnesium and creatinine occurred in some animals at lower doses, but mainly at the two highest doses. These differences from concurrent control were generally mild and non-dose-dependent and were partly reversible. Gastric mucosal lesions, of minimal grade and reversible, were observed in high dose male dogs. Drug-related histopathological changes in the kidney were confined to the juxtaglomerular apparatus of dogs of all telmisartan-treated groups The NOAEL was, therefore, below 5 mg/kg. It should be noted that under steady state conditions, a dose of 5 mg/kg results in mean peak plasma concentrations of 200 and 280 ng/ml, respectively, in male and female dogs (range, 135 to 356 ng/ml in both sexes, Table 3.2.8.3), which are much lower than those encountered in clinical studies at the maximum dose of 160 mg in patients with hypertension (530 to 6000 ng/ml, protocol #502.201).