

absolute, 17% relative to body weight). In males, the increases (same dosage groups) were significant only on a relative to body weight basis. The largest occurred in the group receiving 50/7.8 mg/kg/day (23%).

Statistically significant differences from concurrent control liver, thymus and spleen weights were seen in males only. In each case the finding consisted of lower organ weights when compared to control on an absolute or relative (to brain weight) basis. For liver, this apparent effect of treatment was seen in groups receiving 4.0 or more mg telmisartan/kg/day with the largest effect in the group receiving 50/7.8 mg/kg/day (23% absolute, 21% relative). For thymus, the difference from control was seen only in groups receiving the high dose of telmisartan, the largest effect in the group receiving 50/7.8 mg/kg/day (29% absolute, 26% relative). For spleen, the effect was seen in groups receiving any dose of telmisartan, the largest effect in the group receiving 50/7.8 mg/kg/day (15% absolute, 12% relative).

**TABLE 3.1.1.9**  
SIGNIFICANT ORGAN WEIGHT CHANGES IN MALES AFTER 26 WEEKS OF DOSING

Organ / Tissue	Dose (Telmisartan/HCTZ mg/kg/day)						
	Ctl	0.1/0.03	4.0/1.25	50.0/7.8	50.0/15.6	50.0/0.0	0/15.6
Body Weight (grams)*	521.8	506.5	459.0 ↓	418.0 ↓	431.8 ↓	438.2 ↓	492.4 ↓
HEART absolute (grams)	1.320	1.340	1.140 ↓	1.000 ↓	1.010 ↓	1.050 ↓	1.290
relative (% BW)	0.255	0.266	0.249	0.241 ↓	0.233 ↓	0.239 ↓	0.262
relative (% BrW)	0.575	0.590	0.500 ↓	0.450 ↓	0.448 ↓	0.466 ↓	0.567
KIDNEY absolute (grams)	2.930	2.900	3.060	2.870	2.810	2.880	3.020
relative (% BW)	0.564	0.574	0.667 ↑	0.692 ↑	0.653 ↑	0.658 ↑	0.614 ↑
relative (% BrW)	1.278	1.272	1.343	1.288	1.255	1.283	1.330
LIVER absolute (grams)	17.480	16.80	15.920 ↓	13.430 ↓	14.700 ↓	14.620 ↓	16.560
relative (% BW)	3.349	3.321	3.467	3.225	3.401	3.336	3.365
relative (% BrW)	7.608	7.369	6.990 ↓	6.018 ↓	6.550 ↓	6.551 ↓	7.309
THYMUS absolute (grams)	0.150	0.148	0.133	0.107 ↓	0.114 ↓	0.121 ↓	0.158
relative (% BW)	0.029	0.029	0.029	0.026	0.026	0.028	0.032
relative (% BrW)	0.065	0.065	0.058	0.048 ↓	0.051 ↓	0.054 ↓	0.070
SPLEEN absolute (grams)	0.922	0.828 ↓	0.794 ↓	0.784 ↓	0.797 ↓	0.796 ↓	0.853
relative (% BW)	0.178	0.163	0.173	0.187	0.185	0.182	0.173
relative (% BrW)	0.401	0.363 ↓	0.349 ↓	0.351 ↓	0.354 ↓	0.354 ↓	0.376
ADRENALS absolute (mg) <sup>§</sup>	62.430	66.06	62.500	71.900 ↑	71.650 ↑	66.690	70.990 ↑
relative (% BW)	11.984	13.040	13.622 ↑	17.275 ↑	16.642 ↑	15.185 ↑	14.501 ↑
relative (% BrW)	27.138	29.006	27.432	32.235 ↑	31.941 ↑	29.583	31.364 ↑

\* weight at necropsy

§ relative organ weight has to be multiplied by 10<sup>-3</sup>

↑, ↓ Statistically significant (p < 0.05) when compared with concurrent control

Adrenal weights for male groups treated with HCTZ, alone or in combination with the high dose of telmisartan, were significantly higher than control when compared on an absolute or relative basis (body or brain weight). The largest difference was observed in the group receiving 50/7.8 mg/kg/day (15% absolute, 19% relative to brain weight) (Table 3.1.1.9). For females, the opposite effect was seen (absolute and relative weights lower than control) and appeared to be associated with exposure to telmisartan, rather than HCTZ (telmisartan doses of 4 or more

mg/kg/day). The largest difference from control was observed in the group receiving 50/0 mg/kg/day (14% absolute, 11% relative to brain weight) (Table 3.1.1.10).

TABLE 3.1.1.10  
SIGNIFICANT ORGAN WEIGHT CHANGES IN FEMALES AFTER 26 WEEKS OF DOSING

Organ / Tissue	Dose (Telmisartan/HCTZ mg/kg/day)						
	Ctl	0.1/0.03	4.0/1.25	50.0/7.8	50.0/15.6	50.0/0.0 †	0/15.6
Body Weight (grams)*	271.8	277.3	265.9	269.0	266.5	274.8	275.8
HEART absolute (grams)	0.910	0.900	0.780 ↓	0.780 ↓	0.810 ↓	0.780 ↓	0.900
relative (% BW)	0.337	0.326	0.295 ↓	0.289 ↓	0.304 ↓	0.285 ↓	0.326
relative (% BrW)	0.440	0.435	0.379 ↓	0.376 ↓	0.387 ↓	0.380 ↓	0.430
KIDNEY absolute (grams)	2.000	2.010	2.190 ↑	2.230 ↑	2.300 ↑	2.190 ↑	2.160 ↑
relative (% BW)	0.737	0.727	0.823 ↑	0.830 ↑	0.865 ↑	0.797 ↑	0.785 ↑
relative (% BrW)	0.962	0.968	1.052 ↑	1.080 ↑	1.099 ↑	1.064 ↑	1.037 ↑
LIVER absolute (grams)	10.620	10.520	10.570	10.710	10.470	10.200	10.280
relative (% BW)	3.903	3.792	3.974	3.974	3.933	3.709	3.722
relative (% BrW)	5.110	5.065	5.114	5.186	5.010	4.965	4.923
THYMUS absolute (grams)	0.113	0.127	0.097	0.111	0.109	0.121	0.125
relative (% BW)	0.042	0.046	0.036	0.041	0.041	0.044	0.045
relative (% BrW)	0.054	0.061	0.047	0.054	0.052	0.059	0.060
SPLEEN absolute (grams)	0.619	0.641	0.587	0.653	0.634	0.626	0.625
relative (% BW)	0.228	0.231	0.220	0.243	0.238	0.228	0.227
relative (% BrW)	0.297	0.308	0.284	0.316	0.303	0.305	0.300
ADRENALS absolute (mg) <sup>§</sup>	88.910	86.710	79.820 ↓	78.880 ↓	83.720	76.540 ↓	94.270
relative (% BW)	32.742	31.359	30.023	29.408 ↓	31.445	27.837 ↓	34.108
relative (% BrW)	42.848	41.681	38.666	38.157 ↓	40.081	37.195 ↓	45.161

\* weight at necropsy

§ relative organ weight has to be multiplied by 10<sup>-3</sup>

†, ↓ Statistically significant (p < 0.05) when compared with concurrent control

Among four animals that died or were killed moribund, only three (including one control animal) were necropsied (see Table 3.1.1.1). A female rat given 50 mg telmisartan/kg/day demonstrated liver necrosis, dilated stomach and suspected mucosal erosions. A female given 15.6 mg HCTZ/kg/day died of acute intra-abdominal bleeding. The sponsor contends that none of these deaths are treatment-related.

GI and kidney were considered the principal organs of toxicity in this study. In the glandular stomach (antrum), mucosal injury, consisting of ulcer or erosion, generally accompanied by inflammation, or inflammation alone was observed in both sexes receiving 4 or more mg telmisartan/kg/day with or without HCTZ. The total incidence of the afflicted rats was dose-dependent (Table 3.1.1.11). Rats receiving the high dose combination (50/7.8 or 50/15.6 mg/kg/day telmisartan/HCTZ) developed gastric alterations more often than those that received telmisartan alone (50/0 mg/kg/day) did. The lesions correlated with discoloration of the gastric mucosa noted at necropsy. In two females (one receiving 4/1.25, the other receiving 50/15.6 mg/kg/day telmisartan/HCTZ), the erosions were re-epithelialized, consistent with healing despite continued dosing. Seven rats receiving the high dose of telmisartan, with or without HCTZ, showed focal hyperplasia of the glandular stomach mucosa, indicating regeneration of a

mucosal injury under telmisartan exposure. None of the rats receiving HCTZ alone developed erosions or ulcers in the glandular stomach. The recovery group animals did not demonstrate gastric lesions.

TABLE 3.1.1.11  
INCIDENCE OF GASTROINTESTINAL LESIONS IN RATS AFTER 26 WEEKS OF DOSING

Dose Tel/HCTZ (mg/kg/day)	Ctl		0.1/0.03		4.0/1.25		50.0/7.8		50.0/15.6		50.0/0.0 + 0/15.6		
Sex	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	
# Organs / Tissues Examined	20	20	20	20	20	20	20	20	20	20	20	20	
Number of Animals													
Nonglandular Stomach erosion <sup>a</sup>		1										1	1
Glandular Stomach													
dilatation	12	7	16	6	13	10	5	12	9	11	14	12	10
erosion				2	2	2	5	1	3	4			6
cyst				1	1	1			2		1	1	
inflammation					3		6	3	3	5	4	4	
hyperplasia							2		1	2	1	1	
ulcer										1			
Duodenum											1 <sup>c</sup>		
Cecum									1 <sup>b</sup>			1 <sup>d</sup>	
Rectum													1 <sup>e</sup>

a: the sponsor regards the nonglandular stomach erosion as morphologically equivalent to a non-specific stress response; b: dilatation; c: inflammation; d: one animal developed edema, hemorrhage and congestion in the cecum; e: hemorrhage

Renal findings involved the juxtaglomerular apparatus (JGA) and cortical tubules of rats receiving 4.0 or more mg telmisartan/kg/day with or without HCTZ (Table 3.1.1.12). The alterations of the JGA, according to the sponsor, were pharmacologically mediated and histopathologically characterized by prominent granularity, vacuolation, hypertrophy and hyperplasia of the juxtaglomerular cells. The walls of the cortical arterioles were concomitantly thickened. The total incidence of the afflicted rats was dose-dependent. Also, the severity of the JGA changes increased with the dose level when it was evaluated semi-quantitatively on a + to ++++ scale. Co-administration of HCTZ had no aggravating effect on the development of JGA alterations relative to telmisartan alone. The JGA changes were completely reversible during the recovery period. However, marginal arteriolar thickening was still observed at the end of the 8-week recovery period in 4/10 males and 5/10 females dosed at 50.0/15.6 mg telmisartan-HCTZ/kg/day. Slight to mild proximal tubular atrophy was noted in most of the drug treated animals (at all dose levels) and also in a few control animals. The incidence was dose-dependent. It was frequently associated with minimal interstitial mononuclear infiltration and, in some mid and high dose animals, with regenerative basophilia of tubules. Concomitant administration of HCTZ did not enhance the effect of telmisartan on the development of these alterations. The high dose recovery group still demonstrated a higher incidence of the remnants of this process (i.e., atrophic tubules, interstitial infiltration, thickening) relative to concurrent controls. The sponsor considers the tubular atrophy to be a compound-induced toxic or ischemic alteration only in rats

receiving 50 mg telmisartan/kg/day with or without HCTZ. Other findings in surviving animals belonged to the so-called spontaneous background pathology.

**TABLE 3.1.1.12**  
INCIDENCE OF RENAL PATHOLOGY IN RATS AFTER 26 WEEKS OF DOSING

Dose Tel/HCTZ (mg/kg/day)	Ctl		0.1/0.03		4.0/1.25		50.0/7.8		50.0/15.6		50.0/0.0		0/15.6	
	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 (sacrificed/dead/terminal kill)														
<b>JGA Changes</b>														
Hypertrophy	0	0	0	0	18	16	20	20	20	19	20	19	0	0
Hyperplasia	0	0	0	0	8	4	20	19	20	19	19	14	0	0
Vacuolation	0	0	0	0	7	8	12	8	2	11	10	7	0	0
<b>Arterial thickening</b>					2	2	17	16	18	17	14	8	0	0
<b>Tubular Atrophy</b>	2	0	2	10	2	14	20	20	19	19	17	17	7	11
<b>Tubular Basophilia</b>	0	0	0	0	0	1	1	0	6	0	6	3	0	0
<b>Interstitial Inflammation</b>	3	1	12	3	15	6	20	16	20	14	20	14	15	2
Animals of the Recovery Period														
# Animals examined	10	10							10	10				
Infiltration	5	1							10	7				
Tubular atrophy	1	3							10	9				
Thickening	0	0							4	5				

Oral toxicokinetics of telmisartan combined with HCTZ were determined in satellite groups consisting of 4 male and 4 female rats per treatment group. Peak ( $C_{max}$ ) and total systemic exposure (AUC) to telmisartan were nearly dose proportional for the lower dose groups (0.1 and 4.0 mg) and more than dose-proportional for the higher dose groups. In general, no differences between male and female rats were observed for  $C_{max}$  and AUC. A considerable inter-individual variability in the plasma concentration of telmisartan was observed in all dose groups. Repeated dosing resulted in accumulation, yielding an increase in  $C_{max}$  and  $AUC_{0-24h}$  in week 26 (1.5- to 3.6- fold increase). The coadministration of HCTZ did not influence the plasma concentration of telmisartan (Table 3.1.1.13).

Peak systemic exposure to HCTZ showed dose proportionality for all dose groups and time points. Telmisartan seemed to increase, to some extent, the  $C_{max}$  and  $AUC_{0-24h}$  values of HCTZ. A considerable inter-individual variability was observed in the measured HCTZ plasma concentration.

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**TABLE 3.1.1.13**  
**PHARMACOKINETIC PARAMETERS OF TELMISARTAN AND HCTZ IN RATS DURING THE 26 WEEK TOXICITY STUDY**

Values are expressed as group arithmetic (A) and geometric\* (G) means. Since there were no differences in values between male and female rats, the table summarizes the pooled data (n=4M and 4F). Data for week 13 measurement is not given in the following table, as it did not contribute toward calculation of C<sub>max</sub> or AUC.

Sampling time	Dose mg/kg/d el/HCT	Telmisartan					HCTZ				
		T <sub>max</sub> , h	C <sub>max</sub> (ng/ml)		AUC <sub>0-24h</sub> (ng.h/ml)		T <sub>max</sub> , h	C <sub>max</sub> (ng/ml)		AUC <sub>0-24h</sub> (ng.h/ml)	
		A mean	A mean	G mean	A mean	G mean	A mean	A mean	G mean	A mean	G mean
Wk 1 (Day 1)	0.1/0.03	3.28	4.6	4.3	56.9	55.1	blq	blq	blq	blq	blq
	4.0/1.25	2.25	165.6	154.1	1705.0	1584.0	1.13	122.5	119.0	552.7	548.3
	50/7.8	1.00	7767.0	7334.0	28930.0	27930.0	1.00	715.5	689.0	2344.0	2338.0
	50/15.6	1.13	6669.0	6008.0	30000.0	29300.0	1.00	1673.0	1652.0	5929.0	5876.0
	50.0/0	nm	nm	nm	nm	nm					
	0/15.6						1.25	1294.0	1282.0	4894.0	4854.0
Wk 26 (Day 181)	0.1/0.03	1.38	10.6	10.3	86.3	84.9	blq	blq	blq	blq	blq
	4.0/1.25	1.25	396.4	368.3	2787.0	2766.0	1.00	204.4	194.5	791.0	699.4
	50/7.8	1.00	30560.0	26080.0	76080.0	73820.0	1.00	1308.0	1279.0	4027.0	3943.0
	50/15.6	1.13	18700.0	16650.0	63790.0	62240.0	1.00	2788.0	2722.0	8509.0	8396.0
	50.0/0	1.13	28160.0	26860.0	97040.0	92330.0					
	0/15.6						1.13	2094.0	2059.0	7027.0	7008.0

\*Since pharmacokinetic data obtained in this study followed a log-normal distribution rather than a normal distribution, it is more appropriate to use geometric mean than to use arithmetic mean.

nm: not measured, blq: below the limit of quantitation

In summary, 26-weeks oral concomitant administration of telmisartan and HCTZ to normotensive rats resulted in dose-dependent hypotension at doses of 4 or more mg telmisartan/kg/day. Based on a comparison of blood pressure effects of the highest dose of telmisartan in the presence and absence of HCTZ, it was concluded that the thiazide diuretic potentiated the hypotensive effect of the angiotensin II receptor blocker. Including one control, 4 rats died or were sacrificed in moribund condition; the deaths and conditions leading to sacrifice were not attributed to drug treatment. Body weight gain and food consumption were reduced for both sexes at 4/1.25 or more mg (telmisartan/HCTZ)/kg/day. Dose-dependent significant decreases in erythrocytic parameters, prothrombin time, protein and total glycerol, and increases in BUN, creatinine (high dose groups only), potassium, magnesium and inorganic phosphate were observed in rats receiving 4/1.25 or more mg/kg/day. HCTZ alone had minimal effect on hematological parameters. However, it slightly but significantly increased BUN, and decreased total protein, potassium, magnesium and inorganic phosphate. The values returned to normal at the end of the 8-week recovery period. Dose-dependent, statistically significant decreases in absolute and relative heart weights relative to concurrent control were seen in both sexes receiving 4 or more mg/kg telmisartan. Statistically significant decreases from concurrent control liver (4 or more mg/kg telmisartan), thymus (50 mg/kg telmisartan with or without HCTZ) and spleen weights (at all doses of telmisartan) were observed in males only. HCTZ alone had no significant effect on these organs. Adrenal weights for male groups treated with HCTZ, alone or

in combination with the high dose of telmisartan, were significantly higher than control. In contrast, for females, the weights were significantly lower with exposure to 4 or more mg/kg telmisartan. A significant and dose-related increase in kidney weight, accompanied by renal histopathology, was observed in both sexes at 4/1.25 or more mg/kg/day. Microscopic examination of the kidney revealed arteriolar thickening, tubular atrophy, interstitial infiltration and hyperplasia/hypertrophy of the JGA apparatus at 4/1.25 or more mg/kg/day. The GI tract was the second principal organ of toxicity. At doses of 4/1.25 or more mg/kg/day, gastrointestinal ulceration, erosion and inflammation were observed. HCTZ had no modulating effect on the telmisartan-associated development of the JGA alterations or GI lesions. Though JGA and GI changes were reversed after compound withdrawal, arteriolar thickening and tubular atrophy still persisted. All of the above effects were previously observed in a 26-week study in rats with telmisartan alone (NDA 20,850).

Toxicokinetic parameters revealed an increase in telmisartan plasma levels ( $AUC_{0-24h}$  and  $C_{max}$ ) over the course of the study, suggesting accumulation of drug in the range of 1.5- to 3.6-fold, far less than that observed in a previous telmisartan monotherapy study in rats (6- to 18-fold). HCTZ did not influence the plasma concentration of telmisartan. The no observed effect level for adverse effects in the current study was 0.1/0.03 mg (telmisartan-HCTZ)/kg/day. At this dose, plasma levels of HCTZ were below the limit of quantification and  $C_{max}$  and  $AUC_{0-24h}$  of telmisartan (on day 181) averaged 10 ng/ml and 86 ng.h/ml, respectively. In normotensive human subjects, 7 daily oral doses of 160/25 mg telmisartan/HCTZ (MRHD is 80/12.5 mg/kg/day) achieved a mean telmisartan  $C_{max,SS}$  and  $AUC_{0-24,SS}$  of 2216 ng/ml and 4834 ng.h/ml, respectively (study #502.114). Thus, at the no observed adverse effect level in the rat study, systemic exposure to telmisartan was 222 times lower than human exposure levels on the basis of  $C_{max}$  and 56 times lower on the basis of AUC.

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### 3.1.2. 26-Week Oral Toxicity Study of Telmisartan/HCTZ in Dogs (Study #50028-02, Document #U99-3058) Vol. 17, 18

This GLP study was conducted by the Department of Toxicology and Safety Assessment at Boehringer Ingelheim Pharmaceuticals, Ridgefield, CT, USA, between February 5 and August 9, 1996.

Male and female beagle dogs (*Canis familiaris*) (White Eagle strain) were approximately 8 to 11 months of age and weighed 7.5-12.7 kg at the start of the study. Test substances, telmisartan (lot #8550141) and HCTZ (lot #150788), were each triturated separately with lactose. Hard gelatin capsules containing lactose (control) or each respective triturated test substance were prepared weekly, and the amount filled was determined for each dog based on its assigned dose group and most recently recorded body weight. Test substances were administered concurrently in separate capsules to 4 dogs per sex per group at doses of 0.25/0.08, 1/0.31, 4/0.63 or 4/1.25 mg/kg/day of telmisartan/HCTZ (groups 2 through 5, respectively). Group 6 received 4 mg/kg/day of telmisartan only and group 7 received 1.25 mg/kg/day of HCTZ only. Control animals (group 1) received lactose, at the same mg/kg/day dose level as the group receiving the highest total amount of drug (group 5). Animals were housed individually in kennels. A fixed amount of certified dog chow was given daily except overnight prior to blood collection and necropsy. Drug-related decreases in food consumption in high dose groups (4 through 6) necessitated changes to canned dog food, in lieu of dog chow, for some of the animals.

The doses were selected on the basis of an 8 week range finding study in which the principal target organs were the kidneys and GI tract. Degenerative changes in cortical and/or medullary tubular epithelium of the kidneys were noted in males and/or females given 24.0/7.5 or 48.0/7.5 mg/kg/day telmisartan/HCTZ. The one male and one female dog in each of these groups were sacrificed on drug day 10 and 12 due to "excessive toxicity." The same animals showed degenerative, inflammatory and hemorrhagic changes in the stomach, small and/or large intestine, myocardium, and thyroid, all changes considered secondary to the renal changes and "resultant renal compromise." A pair of (one male and one female) dogs given 12.0/1.9 mg/kg/day were removed from treatment after 2 days due to "excessive toxicity," after which they were placed on a regimen of 6.0/1.0 mg/kg/day. Hypertrophy and hyperplasia of the juxtaglomerular apparatus, increases in BUN, and decreased hematological parameters were noted in all dosage groups (doses as low as 1.6/0.25 mg/kg/day telmisartan/HCTZ).

#### Observations and Measurements

Clinical Observations: at least twice daily on working days (once on non-working days and once pretest).

Water Consumption: daily.

Body Weight: weekly.

Food Consumption: daily.

Blood Pressure (indirect): weeks -2 (prestudy), 3, 7, 11, 17 and 23 at 2 hr after administration.

Heart Rate and ECG: weeks -2 (prestudy), 5, 8, 12, 18 and 23 (2 hr after administration.)

Ophthalmoscopic Examination: week -4, -1 and during study weeks 3, 7, 11, 16 and 25.

Hematology and Clinical Chemistry: weeks -3, -1, 2 (clinical chemistry only), 4, 8, 12, 18 and 26 (also measured plasma renin activity). Blood samples were collected from the jugular vein of conscious animals after an overnight fast.

Urinalysis: weeks -3, -1, 4, 8, 12, 18 and 26 (collected overnight)

Plasma Telmisartan and HCTZ levels: study days 1, 6, 15 and 26 (at 0, 0.5, 1, 2, 3, 8, 12 and 24 hr postdose). Blood samples were collected from the jugular vein of conscious animals after an overnight fast.

Gross Pathology: A complete necropsy was performed on all (terminal and moribund sacrificed) animals and all macroscopic changes were recorded.

Histopathology: The following organs or tissues were collected from all animals on study and microscopically examined (Table 3.1.2.1). Organs from moribund sacrificed animals were not weighed.

TABLE 3.1.2.1  
TISSUES/ORGANS SAMPLED FOR HISTOPATHOLOGICAL EXAMINATION

Adrenals*	Lymph nodes -bronchial	Spleen
Aorta	-mandibular	sternebra with marrow
Brain*	-mesenteric	Stomach - cardia
Cervix	Ovaries*	- fundus
Esophagus	Pancreas	- pylorus
Eyes with optic nerves	Parotids	Testes with epididymides*
Gall bladder	Pituitary*	Thymus*
Heart*	Prostate	Thyroid/parathyroid glands*
Intestine-large	Rib with marrow	Tongue
Intestine-small	Salivary gland (mandibular)	Tonsils
Kidneys*	Sciatic nerve	Trachea
Liver*	Skeletal muscle (gastrocnemius)	Urinary bladder
Lungs with bronchi	Skin with mammary gland	Uterus
	Spinal cord (thoracolumbar)	Vagina

\*organ weighed

## Results

Two animals receiving 4/1.25 mg/kg/day telmisartan/HCTZ were sacrificed in a moribund state, a male on day 40 and a female on day 180. Prior to sacrifice, the male displayed decreased motor activity, pale gums and decreased rectal temperature, and the female displayed decreased motor activity, mouth ulcerations, dehydration, tremors, and decreased rectal temperature.

Clinical signs of toxicity attributed to test compound were observed in groups dosed at 4/0.63, 4/1.25 and 4.0/0 mg/kg/day of telmisartan/HCTZ. These included dehydration, decreased motor activity, erythema, erosions/ulcerations in the mouth, increased capillary refill time, pale gums, emesis, tremors, hypothermia and anorexia. Occult blood in emesis and fecal samples was observed at a higher frequency in animals receiving the high dose combination of telmisartan and HCTZ (two animals tested positive for blood in stool and emesis) and was considered drug-related. Blood was detected in fecal samples from animals in control, 0.25/0.08, 1/0.31, 4/1.25, 4/0 and 0/1.25 mg/kg/day groups with incidences of 1/8, 2/8, 1/8, 3/8, 1/8 and 1/8 animals, respectively. Emesis from animals in 0.25/0.08, 4/1.25 and 0/1.25 mg/kg/day groups tested positive for occult blood with incidences of 1/8, 4/8 and 1/8 animals, respectively.

There were no significant variations in body weight or body weight gain that could be attributed to drug treatment (Tables 3.1.2.2 and 3.1.2.3, Fig. 3.1.2.1. and 3.1.2.2). However, drug-related decreases in body weight and body weight gain that paralleled reductions in food consumption were observed in individual animals at dosage levels of 4/0.63 (4 females), 4/1.25 (a male and a female) and 4.0/0 mg/kg/day (2 females) telmisartan/HCTZ. Mean food consumption was decreased significantly in females receiving 1/0.31 and 4.0/0.63 mg/kg/day telmisartan/HCTZ at various times during the study.

**TABLE 3.1.2.2**  
EFFECT OF TELMISARTAN WITH OR WITHOUT HCTZ ON BODY WEIGHT AND BODY WEIGHT GAIN  
IN 26 WEEK TOXICITY STUDY IN MALE DOGS

Study wk	Body weight change parameters	Dose: Telmisartan/HCTZ mg/kg/day						
		Control	0.25/0.08	1/0.31	4/0.63	4/1.25	4/0	0/1.25
-1	Mean absolute b. wt., kg	10.4	11.1	11.0	11.0	10.9	11.0	11.4
	Deviation of b. wt. <sup>§</sup>	-	7	6	6	5	6	10
13	Mean absolute b. wt., kg	11.1	12.0	11.6	11.5	11.3	11.4	11.8
	Deviation of b. wt. <sup>§</sup>	-	8	5	4	2	3	6
	B. wt. gain (%) <sup>¶</sup>	7	8	5	5	4	4	4
26	Mean absolute b. wt., kg	11.3	12.5	12.0	11.8	12.1	12.1	12.4
	Deviation of body wt. <sup>§</sup>	-	11	6	4	7	7	10
	B. wt. gain (%) <sup>¶</sup>	9	13	9	7	11	10	9

§ : relative to control (%); There were no statistically significant changes as compared to controls.

¶ : percent increase relative to start of administration; calculations done using means presented above.

**TABLE 3.1.2.3**  
EFFECT OF TELMISARTAN WITH OR WITHOUT HCTZ ON BODY WEIGHT AND BODY WEIGHT GAIN  
IN 26 WEEK TOXICITY STUDY IN FEMALE DOGS

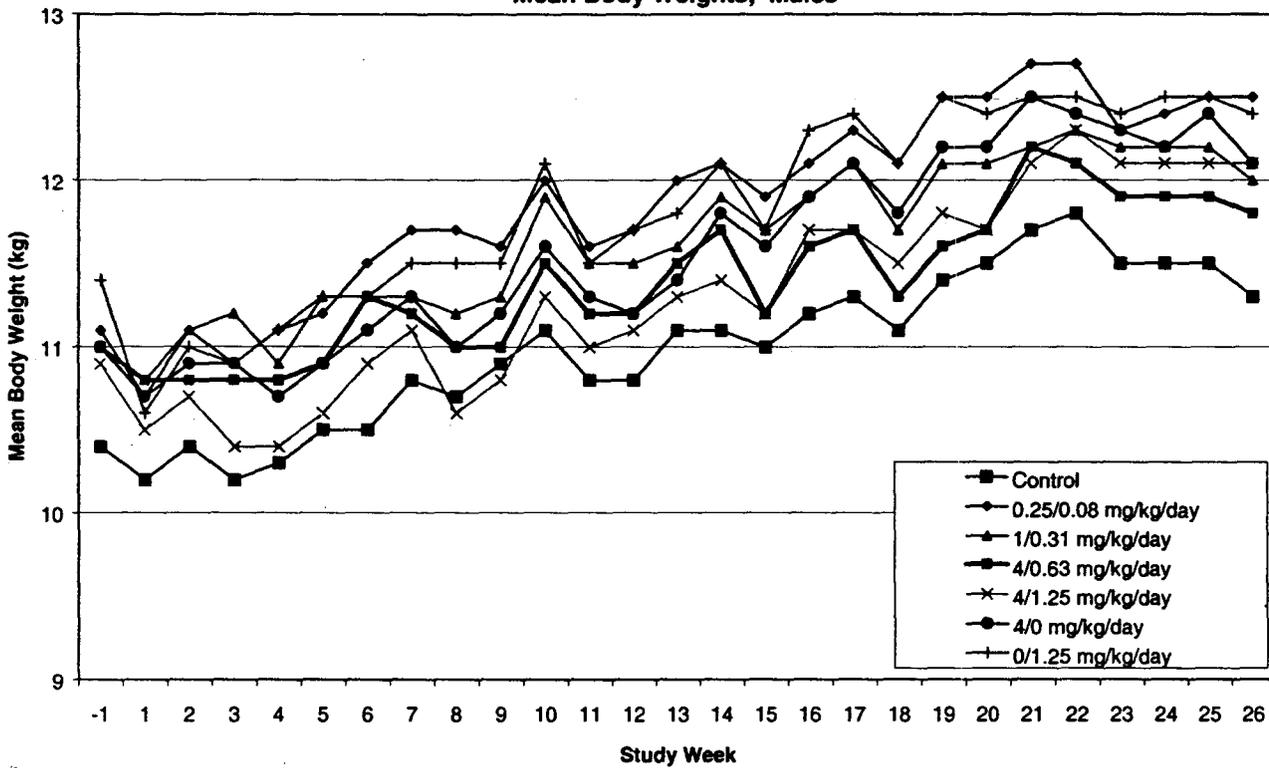
Study wk	Body weight change parameters	Dose: Telmisartan/HCTZ mg/kg/day						
		Control	0.25/0.08	1/0.31	4/0.63	4/1.25	4/0	0/1.25
-1	Mean absolute b. wt., kg	8.4	9.4	9.4	9.2	9.1	9.7*	8.9
	Deviation of b. wt. <sup>§</sup>	-	12	12	10	8	15	6
13	Mean absolute b. wt., kg	10.2	10.5	10.3	10.0	9.8	10.4	10.0
	Deviation of b. wt. <sup>§</sup>	-	3	1	-2	-4	2	-2
	B. wt. gain (%) <sup>¶</sup>	21	12	10	9	8	7	12
26	Mean absolute b. wt., kg	10.4	10.8	11.0	10.0	10.3	10.3	9.9
	Deviation of b. wt. <sup>§</sup>	-	4	6	-4	-1	-1	-5
	B. wt. gain (%) <sup>¶</sup>	24	15	17	9	13	6	11

§ : relative to control (%)

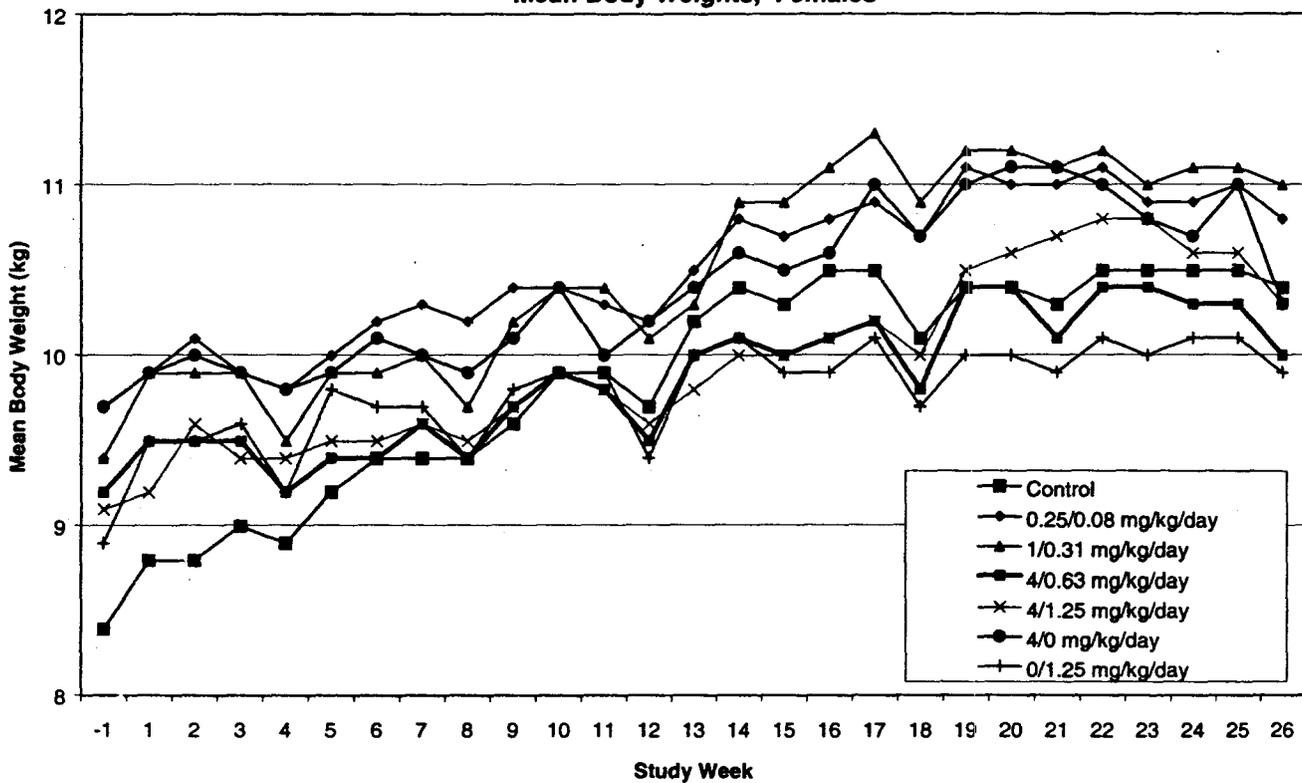
¶ : percent increase relative to start of administration; calculations done using means presented above.

\* : Significantly different as compared to control using a Duncan's multiple range test.

**Fig. 3.1.2.1.: 26-Week Toxicity Study in Dogs on Telmisartan/HCTZ  
Mean Body Weights, Males**



**Fig. 3.1.2.2.: 26-Week Toxicity Study in Dogs on Telmisartan/HCTZ  
Mean Body Weights, Females**



No drug-related changes in heart rate or ECGs were evident in any dose groups. Statistically and biologically significant decreases in mean indirect systolic and/or diastolic blood pressure were noted at dose levels of 0.25/0.08 or more mg/kg/day telmisartan/HCTZ as compared to control animals at various time points during the study. No statistically significant changes in mean blood pressure were observed in animals receiving HCTZ alone as compared to controls.

Statistically significant decreases in mean RBC count, hemoglobin, and hematocrit were observed in animals receiving 1/0.31 (females), 4/0.63 (males and females), 4/1.25 (males and females) and 4/0 (females) mg/kg/day telmisartan/HCTZ. Decreases were not noted in animals treated with HCTZ alone (Table 3.1.2.4).

**TABLE 3.1.2.4**  
EFFECT OF TELMISARTAN WITH OR WITHOUT HCTZ ON HEMATOLOGY IN 26 WEEK TOXICITY STUDY IN DOGS

Parameter	Wk	Sex	Dose (Telmisartan/HCTZ mg/kg/day)													
			Ctl		0.25/0.08		1/0.31		4/0.63		4/1.25		4/0		0/1.25	
			mean	mean	Δ%	mean	Δ%	mean	Δ%	mean	Δ%	mean	Δ%	mean	Δ%	
Erythrocytes (10 <sup>6</sup> /μl)	4	M	6.85	6.44	-6	6.30	-8	6.31	-8	6.21	-9	6.53	-5	6.63	-3	
		F	7.51	7.12	-5	6.43	-14	7.05	-6	6.58*	-12	6.68*	-11	7.47	-1	
	8	M	6.81	6.80	0	6.37	-6	5.87	-14	5.37*	-21	6.35	-7	6.84	0	
		F	7.20	6.90	-4	5.86	-19	6.37	-12	5.67*	-21	6.27	-13	7.46	4	
	12	M	7.24	6.78	-6	6.78	-6	6.09*	-16	5.50*	-24	6.32	-13	7.19	-1	
		F	7.33	6.93	-5	6.65	-9	5.97*	-19	5.57*	-24	6.14*	-16	7.61	4	
	18	M	7.28	7.27	0	7.01	-4	6.58	-10	6.26	-14	6.64	-9	7.11	-2	
		F	7.80	7.04	-10	6.69*	-14	6.35*	-19	5.88*	-25	6.30*	-19	7.71	-1	
26	M	7.26	7.85	8	7.39	2	6.93	-5	6.36	-12	7.21	-1	7.62	5		
	F	7.81	6.97	-11	6.70*	-14	6.93	-11	6.07	-22	7.32	-6	8.28	6		
Hemoglobin (g/dL)	4	M	15.5	14.8	-5	14.1	-9	14.3	-8	14.3	-8	15.0	-3	15.4	-1	
		F	17.0	16.1	-5	14.6*	-14	16.5	-3	15.3*	-10	15.7	-8	17.4	2	
	8	M	15.7	15.5	-1	14.6	-7	13.3*	-15	12.6*	-20	14.6	-7	15.7	0	
		F	16.6	15.6	-6	13.3*	-20	15.0	-10	13.3*	-20	14.8	-11	17.0	2	
	12	M	16.5	15.5	-6	15.3	-7	13.8*	-16	13.1*	-21	14.5	-12	16.2	-2	
		F	16.6	15.7	-5	15.1	-9	14.0*	-16	13.0*	-22	14.6*	-12	17.2	4	
	18	M	16.9	16.8	-1	15.9	-6	15.2	-10	15.1	-11	15.6	-8	16.4	-3	
		F	18.0	16.3	-9	15.3*	-15	15.3*	-15	14.3*	-21	15.2*	-16	18.0	0	
26	M	16.1	17.2	7	16.0	-1	15.0	-7	14.7	-9	16.0	-1	16.8	4		
	F	17.2	15.2	-12	14.9	-13	15.9	-8	13.8*	-20	16.8	-2	18.3	6		
Hematocrit (%)	4	M	46.6	43.7	-6	41.7	-11	41.9	-10	42.0	-10	43.9	-6	45.3	-3	
		F	50.5	47.7	-6	42.7*	-15	48.1	-5	45.1	-11	46.3	-8	50.5	0	
	8	M	46.8	46.9	0	43.2	-8	39.8*	-15	37.7*	-19	43.5	-7	47.0	0	
		F	49.1	46.9	-4	39.6*	-19	44.0	-10	39.5*	-20	44.7	-9	50.7	3	
	12	M	49.0	46.2	-6	45.8	-7	40.9*	-17	38.6*	-21	43.2	-12	48.3	-1	
		F	49.7	46.9	-6	45.8	-8	42.1*	-15	39.1*	-21	43.4*	-13	51.4	3	
	18	M	48.7	49.0	1	46.2	-5	43.9	-10	44.0	-10	45.4	-7	47.0	-3	
		F	52.1	46.9	-10	44.8*	-14	44.6*	-14	41.3*	-21	44.2*	-15	51.6	-1	
26	M	47.7	52.2	9	47.4	-1	44.6	-6	42.9	-10	47.2	-1	50.2	5		
	F	50.9	44.5	-13	43.9	-14	46.2	-9	40.7*	-20	50.0	-2	54.0	6		

\* Statistically significant as compared to control, using a Duncan's multiple-range test.

Dose-dependent increases in blood urea nitrogen were noted at 1/0.31, 4/0.63 ( $p < 0.05$  at this dose only), 4/1.25 and 4/0 mg/kg/day telmisartan/HCTZ. The presence of HCTZ appeared to exacerbate the effect. Severe increases in BUN (194 and 284 mg/dL vs. average concurrent control values of 15 mg/dL) and creatinine (12.1 and 13.8 mg/dL vs. average control values of 0.8 mg/dL) in one female (measured in drug week 26) and one male (measured in drug week 6) receiving 4/1.25 mg/kg/day telmisartan/HCTZ necessitated early sacrifices of these animals. Creatinine levels were occasionally elevated in the mid and high dose combination groups but were not statistically significantly higher than concurrent control at most time points of measurement (Table 3.1.2.5). Slight and non-significant increases in magnesium values were

**TABLE 3.1.2.5**  
EFFECT OF TELMISARTAN WITH OR WITHOUT HCTZ ON BLOOD CHEMISTRY DURING 26 WEEK TOXICITY STUDY IN DOGS  
(Results expressed as group mean values)

Parameter	Wk	Sex	Dose (Telmisartan/HCTZ mg/kg/day)													
			Ctl		0.25/0.08		1/0.31		4/0.63		4/1.25		4/0		0/1.25	
			mean	Δ%	mean	Δ%	mean	Δ%	mean	Δ%	mean	Δ%	mean	Δ%	mean	Δ%
BUN (mg/dL)	2	M	14	13	-7	19	36	21	50	32	129	21	50	14	0	
		F	15	17	13	19	27	48*	220	40	167	21	40	16	7	
	4	M	15	14	-7	18	20	25*	67	35	133	22	47	13	-13	
		F	15	16	7	21	40	45*	200	47	213	25	67	18	20	
	8	M	15	13	-13	18	20	24*	60	27	80	22	47	14	-7	
		F	14	16	14	20	43	34*	143	41	193	29	107	17	21	
	12	M	13	13	0	17	31	25*	92	34	162	29	123	13	0	
		F	15	16	7	17	13	37*	147	42	180	32	113	16	7	
	18	M	14	12	-14	17	21	25*	79	30	114	24	71	15	7	
		F	15	16	7	23	53	40*	167	43	187	24	60	17	13	
	26	M	17	14	-18	17	0	27	59	33	94	27	59	16	-6	
		F	17	19	12	24	41	51	200	74	335	44	159	18	6	
	Creati- nine (mg/dL)	2	M	0.9	0.8	-11	0.9	0	0.9	0	0.9	0	0.8	-11	0.8	-11
			F	0.8	0.9	13	0.9	13	1.1*	38	1.0	25	0.9	13	0.9	13
		4	M	0.8	0.8	0	0.8	0	0.9	13	1.0*	25	0.8	0	0.7	-13
			F	0.8	0.8	0	0.9	13	1.0	25	0.9	13	0.9	13	0.9	13
8		M	0.9	0.8	-11	0.9	0	0.9	0	0.9	0	0.9	0	0.8	-11	
		F	0.8	0.8	0	0.9	13	1.0	25	1.0	25	1.0	25	0.9	13	
12		M	0.9	0.9	0	0.9	0	1.0	11	0.9	0	1.0	11	0.8	-11	
		F	0.9	0.9	0	0.9	0	1.1	22	1.0	11	1.0	11	0.9	0	
18		M	0.9	0.8	-11	0.8	-11	1.0	11	0.9	0	0.9	0	0.8	-11	
		F	0.9	0.8	-11	0.9	0	1.1	22	1.1	22	0.8	-11	0.9	0	
26		M	1.0	0.9	-10	0.9	-10	1.1	10	0.9	-10	1.1	10	0.9	-10	
		F	0.9	0.8	-11	0.9	0	1.4	56	3.7	311	1.3	44	0.9	0	

\* Statistically significant as compared to control, using a Duncan's multiple-range test.

observed in all animals of the high dose group. Increases in plasma renin activity were noted in individual animals of all dose groups except HCTZ alone; statistical significance as compared to control was noted only for males in the high dose group. The magnitude of the increase in PRA was not clearly dose related. No drug-related changes in urinalysis were observed in the study.

The evaluation of drug effects on organ weights was based on relative organ weights (relative to body weight or brain weight) due to large differences in absolute body weight of the animals across groups. At the 26 week sacrifice, mean relative heart weights for all treated groups excluding HCTZ alone were 12-16% lower than concurrent control but none of these differences were statistically significant (Table 3.1.2.6). A slightly but significantly higher than control relative kidney weight was noted for females in higher dosage groups with or without HCTZ (Table 3.1.2.7). Small decreases (relative to concurrent control) in relative thyroid weight were significant for males dosed at 4 mg telmisartan/kg/day with or without HCTZ.

**TABLE 3.1.2.6**  
TELMISARTAN ASSOCIATED ORGAN WEIGHT FINDINGS IN MALE DOGS

Organ / Tissue	Dose (Telmisartan/HCTZ mg/kg/day)						
	Ctl	0.25/0.08	1/0.31	4/0.63	4/1.25	4/0	0/1.25
Body Weight (kilograms)*	11.2	12.0	11.6	11.4	11.6	11.9	12.2
HEART absolute (grams)	94.7	88.5	83.5	80.9	84.2	87.5	94.3
relative (% BW)	0.843	0.741	0.733	0.712	0.723	0.739	0.782
relative (% BrW)	115.4	113.9	104.7	103.7	99.1	107.4	111.0
KIDNEY absolute (grams)	47.6	51.7	47.4	47.1	52.2	50.2	54.0
relative (% BW)	0.426	0.431	0.416	0.414	0.448	0.422	0.445
relative (% BrW)	58.2	66.3	59.6	60.3	61.6	61.2	63.0
THYROID absolute (grams)	1.072	1.003	1.006	0.844	0.849	0.801↓	0.956
relative (% BW)	0.00962	0.00836	0.00873	0.00738↓	0.00732↓	0.00679↓	0.00786
relative (% BrW)	1.310	1.284	1.265	1.076	1.002	0.986	1.120

**TABLE 3.1.2.7**  
TELMISARTAN ASSOCIATED ORGAN WEIGHT FINDINGS IN FEMALE DOGS

Organ / Tissue	Dose (Telmisartan/HCTZ mg/kg/day)						
	Ctl	0.25/0.08	1/0.31	4/0.63	4/1.25	4/0	0/1.25
Body Weight (kilograms)*	10.4	10.8	11.0	9.5	10.1	10.2	9.9
HEART absolute (grams)	71.1	70.2	70.7	68.4	65.4	72.5	79.6
relative (% BW)	0.699	0.649	0.645	0.722	0.632	0.712	0.812
relative (% BrW)	94.7	90.8	92.4	90.9	85.8	85.7	107.2
KIDNEY absolute (grams)	38.2	43.7	41.5	44.4	43.6	49.5↑	41.4
relative (% BW)	0.376	0.406	0.380	0.467↑	0.422	0.487↑	0.422
relative (% BrW)	51.3	55.7	54.5	59.0	57.1	58.5	55.5
THYROID absolute (grams)	0.808	0.971	0.907	0.671	0.760	0.774	0.775
relative (% BW)	0.00793	0.00904	0.00824	0.00706	0.00718	0.00781	0.00789
relative (% BrW)	1.083	1.257	1.199	0.892	1.012	0.921	1.054

\* weight at necropsy, fasted

↑, ↓ Statistically significant when compared with concurrent control, using a Duncan's multiple range test.

Treatment-related macroscopic findings (gastrointestinal erosions and ulcers of the tongue and esophagus) were largely restricted to the two high dose moribund sacrificed animals.

Treatment-related histopathological findings were largely restricted to the kidneys. The sponsor classifies the effects into two types, toxic and pharmacological. The toxic effect noted in the kidney consisted of renal cortical nephropathy. The underlying renal lesions consisted of cortical tubular nephrosis in which cortical tubules were dilated and the tubule cells had become atrophic and were undergoing degeneration. It was observed in the kidneys of two females receiving 4/0.63 mg/kg/day, a male and a female (both sacrificed moribund) receiving 4/1.25 mg/kg/day and a female receiving 4/0 mg/kg/day telmisartan/HCTZ (Table 3.1.2.8). The pharmacological finding was characterized by the development of hyperplasia/hypertrophy of the afferent arteriole in the juxtaglomerular apparatus. It was found to be prominent in both sexes receiving 1.0 or more mg telmisartan/kg/day with or without HCTZ (Table 3.1.2.8). Also seen in the two high dose moribund sacrificed animals were cortical lymphoid depletion in the thymus and mesenteric lymph nodes and mineralization of the heart (Table 3.1.2.9).

TABLE 3.1.2.8

INCIDENCE OF DRUG-RELATED RENAL PATHOLOGY IN DOGS AFTER 26 WEEKS OF DOSING

Dose Level (mg/kg/day)	Ctl		0.25/0.08		1/0.31		4/0.63		4/1.25		4/0		0/1.25	
	M	F	M	F	M	F	M	F	M	F	M	F	M	F
Sex														
# Animals per Group	4	4	4	4	4	4	4	4	4	4	4	4	4	4
# Organs/ Tissues Examined	4	4	4	4	4	4	4	4	4	4	4	4	4	4
Number of Animals (sacrificed/dead/terminal kill)														
JGA hyperplasia					4	1	4	4	3	4	3	3		
Cortical Tubular Dilatation								2	1 <sup>a</sup>	1 <sup>b</sup>		1		
Medullary Tubule dilatation										1 <sup>b</sup>				
Cortical luminal material										1 <sup>b</sup>				
Cortical tubule basophilia										1 <sup>b</sup>				
Cortical tubule degeneration									1 <sup>a</sup>	1 <sup>b</sup>				
Cortical infiltrate-subtle										1 <sup>b</sup>				

Note: a = associated with moribund sacrifice male in Drug Week 6

b = associated with moribund sacrifice female in Drug Week 26.

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**TABLE 3.1.2.9**  
**INCIDENCE OF LESIONS CONSIDERED SECONDARY TO DRUG-EFFECTS IN DOGS**  
**AFTER 26 WEEKS OF DOSING**

Dosage (mg/kg/day)	Ctl		0.25/0.08		1/0.31		4/0.63		4/1.25		4/0		0/1.25	
	M	F	M	F	M	F	M	F	M	F	M	F	M	F
Sex														
# Animals per Group	4	4	4	4	4	4	4	4	4	4	4	4	4	4
# Organs / Tissues Examined	4	4	4	4	4	4	4	4	4	4	4	4	4	4
Number of Animals														
Colon: dilatation, glandular												1 <sup>b</sup>		
Esophagus: erosion, mucosal												1 <sup>b</sup>		
Stomach:														
erosion, mucosal										1 <sup>a</sup>				
mineralization, mucosal										1 <sup>a</sup>				
mineralization, transmural										1 <sup>a</sup>				
mucosal regeneration											1 <sup>b</sup>			
Tongue														
glossitis, acute										1 <sup>a</sup>	1 <sup>b</sup>			
infiltrate, epithelial										1 <sup>a</sup>				
Lip: cheilitis, ulcerative											1 <sup>b</sup>			
Heart: mineralization, intimal										1 <sup>a</sup>				
Liver: infiltrate, parenchymal, mix														1
Lymph node, mesenteric														
Depletion, lymphocytic, cortical										1 <sup>a</sup>	1 <sup>b</sup>			

Note: a = associated with moribund sacrifice male in Drug Week 6  
 b = associated with moribund sacrifice female in Drug Week 26.

Toxicokinetic investigations showed higher (statistically not significant) plasma mean telmisartan AUC<sub>0-24h</sub> and C<sub>max</sub> values for female than for male dogs in all dose groups except the high dose telmisartan (only) group. The time to C<sub>max</sub> ranged from 1 to 3 hours. The concurrent administration of HCTZ did not affect telmisartan AUC or C<sub>max</sub> values after single or multiple dose administration. For HCTZ, there was an increase in median AUC for both male and female dogs with an increase in dose up to 1.25 mg/kg/day. For most of the dose groups, both AUC and C<sub>max</sub> values in females tended to be higher (statistically not significant) than in males. The time to C<sub>max</sub> ranged from 1 to 2 hours. There was no effect of telmisartan on levels of HCTZ after multiple dose administration. In contrast, concurrent single dose administration of telmisartan decreased AUC or C<sub>max</sub> values of HCTZ in both male and female dogs (Table 3.1.2.11). A considerable interindividual variability was observed in the measured telmisartan and HCTZ plasma concentrations.

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**TABLE 3.1.2.11**  
**PHARMACOKINETIC PARAMETERS OF TELMISARTAN AND HCTZ IN DOGS DURING THE 26 WEEK TOXICITY STUDY**

Values are expressed as group arithmetic (A) and geometric (G) means.  $C_{max}$  values presented are the means of individual animal  $C_{max}$ , with each sex presented separately.

Sampling time	Dose (mg/kg/d) Tel/HCT	Sex	Telmisartan				Hydrochlorothiazide			
			$C_{max}$ (ng/ml)		AUC <sub>0-24h</sub> (ng.h/ml)		$C_{max}$ (ng/ml)		AUC <sub>0-24h</sub> (ng.h/ml)	
			A mean	G mean	A mean	G mean	A mean	G mean	A mean	G mean
Week 1 (Day 1)	0.25/0.08	M	0	NC	0	NC	14	13	84	83
		F	4	NC	15	NC	39	28	104	98
	1/0.31	M	47	40	352	323	132	103	482	465
		F	52	41	321	280	109	84	404	377
	4/0.63	M	344	259	1712	1642	316	205	1108	1049
		F	320	298	2477	2349	278	250	951	901
	4/1.25	M	259	234	1322	1252	197	188	1113	1102
		F	248	234	2596	2414	211	184	1304	1273
	4/0	M	539	479	2206	1984				
		F	248	236	1774	1682				
0/1.25	M					433	308	1867	1718	
	F					615	608	2057	2040	
Week 26 (Day 179)	0.25/0.08	M	0	NC	3	NC	13	11	75	73
		F	17	22	81	101	48	43	125	115
	1/0.31	M	54	52	608	583	120	74	433	417
		F	114	104	701	668	137	120	420	403
	4/0.63	M	432	346	1650	1636	211	166	846	812
		F	905	810	4914	4197	588	563	2435	2182
	4/1.25	M	577	462	2701	2595	563	414	2014	1966
		F	748	698	5678	4767	887	442	9252	2792
	4/0	M	673	650	2983	2673				
		F	677	647	4229	3609				
0/1.25	M					542	322	1883	1634	
	F					942	838	2173	2106	

NC = not calculated because most values were zero.

Note: Maximum concentrations of telmisartan were generally reached 1-3 hours after administration, while maximum concentrations of hydrochlorothiazide were reached 1-2 hours after administration.

In summary, oral administration of telmisartan/HCTZ to dogs at 0.25/0.08, 1/0.31, 4/0.63, 4/1.25 and 4/0 mg/kg/day for 26 weeks resulted in significant reductions in indirect blood pressure. HCTZ (1.25 mg/kg/day) alone did not significantly affect the mean blood pressure. Two high dose combination group animals failed to complete the study (moribund sacrificed) with evidence of renal toxicity (cortical tubular nephropathy). In addition, GI erosions and ulcers of the tongue and esophagus, and mineralization of the heart were seen in these two moribund animals. Evidence of cortical tubular dilatation, accompanied by various degrees of cortical tubule cell atrophy and degeneration, was observed in three terminal sacrifice animals, two receiving 4/0.63 and one receiving 4/0 mg/kg/day of telmisartan/HCTZ. HCTZ alone was not toxic but increased the nephrotoxicity observed with telmisartan. It should be noted that HCTZ did not influence the concentration of telmisartan in plasma. The exaggerated pharmacological effect characterized by the development of hyperplasia/hypertrophy of the afferent arteriole in the juxtaglomerular apparatus was displayed in both sexes receiving 1.0 or more mg telmisartan/kg/day with or without HCTZ. The no observed toxic effect level for the combination of telmisartan and HCTZ in dogs was considered to be 0.25/0.08 mg/kg/day. At this dose, mean

telmisartan  $C_{max}$  and  $AUC_{0-24hr}$  were, respectively, 8 ng/ml and 42 ng.h/ml (male and female combined at week 26). In normotensive human subjects, 7 daily oral doses of 160/25 mg telmisartan/HCTZ (MRHD is 80/12.5 mg/kg/day) achieved a mean telmisartan  $C_{max,SS}$  and  $AUC_{0-24,SS}$  of 2216 ng/ml and 4834 ng.h/ml, respectively (study #502.114). Thus, at the no observed adverse effect level in the dog study, systemic exposure to telmisartan was 277 times lower than human exposure levels on the basis of  $C_{max}$  and 115 times lower on the basis of AUC.

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### 3.2. Reproductive Toxicity Study

#### 3.2.1. Developmental Toxicity Study in Rats (Study #96B030, Doc #U97-2733) Vol. 9

This GLP study, conducted by [redacted] investigated the effect of combined administration of telmisartan and HCTZ on embryonic/fetal development. Dosing initiated on April 22, 1996.

Animals: Presumed pregnant female rats (Chbb:THOM (SPF)) were approximately 12 weeks of age and weighed 213.3-281.2 gm at initiation of dosing.

Mode of Administration/Dosage Levels: Suspensions of telmisartan (batch #8550141) were prepared daily in 0.5% hydroxyethylcellulose. HCTZ (batch #150788/924950) was added to the suspension prior to dosing. The mixture was administered orally by gavage (10 ml/kg), once daily, to three groups of 24 mated females each at (telmisartan/HCTZ) doses of 3.2/1.0, 15/4.7 or 50/15.6 mg/kg/day (groups 1, 2 and 3, respectively) on gestational days 7 through 16. An additional group (group 4) received only HCTZ (15.6 mg/kg/day). Control animals (group 0) received the vehicle in a similar manner. The study lacked a telmisartan (only) group. A satellite group (n=6) was included with each dose group (1 through 4) for toxicokinetics.

The doses were selected on the basis of a previous developmental toxicity study with telmisartan alone (see section 3.5.2. reviewed under NDA #20,850). In that study, an oral dose of 50 mg telmisartan/kg/day did not affect reproduction capability or progeny. However, the maternal NOAEL was below 5 mg/kg/day (a 3.4% reduction in body weight and a 10% reduction in body weight gain were observed at this dose,  $p < 0.05$ ).

Observations/Measurements: All animals were observed for physical signs twice daily (once on weekends). Body weights were recorded on days 1, 7-16 and 21 of gestation. Food consumption was determined on gestation days 7, 14 and 21. For toxicokinetics study, blood samples were collected *via* the retrobulbar venous plexus from halothane anesthetized satellite animals (n=6) in all dose groups including control before treatment and 1, 3 and 6 hr post treatment on gestation day 16.

On gestation day 22, all surviving females were sacrificed under pentobarbital anesthesia and were examined for number of corpora lutea, number and position of implantation sites and early or late resorptions. All fetuses were examined externally, weighed, sexed and classified as dead or alive. Approximately half of all fetuses from each litter were randomly selected, eviscerated and processed for skeletal examinations. The remaining fetuses were prepared for visceral examination.

Results: There were no deaths. No clinical signs were observed in the study except for a dam in the 15.0/4.7 mg/kg/day telmisartan/HCTZ group. This animal exhibited vaginal bleeding after 8 administrations and resorptions at hysterectomy.

In all treated groups, significant and dose-dependent decreases in body weight gain (relative to concurrent control) were noted. A statistically significant decrease in body weight gain was observed as early as after 2 dose administrations in mid and high dose combination groups. The body weight tended to return normal in all dose groups except for the high dose combination group ( $p < 0.05$ ) after cessation of treatment (GD 21) (Table 3.2.1.1). In the 15.6 mg HCTZ/kg/day group, body weight gain was slightly but significantly decreased on GDs 12 and 15 but was similar to control just before cessation of treatment (Fig. 3.2.1.1, Table 3.2.1.1).

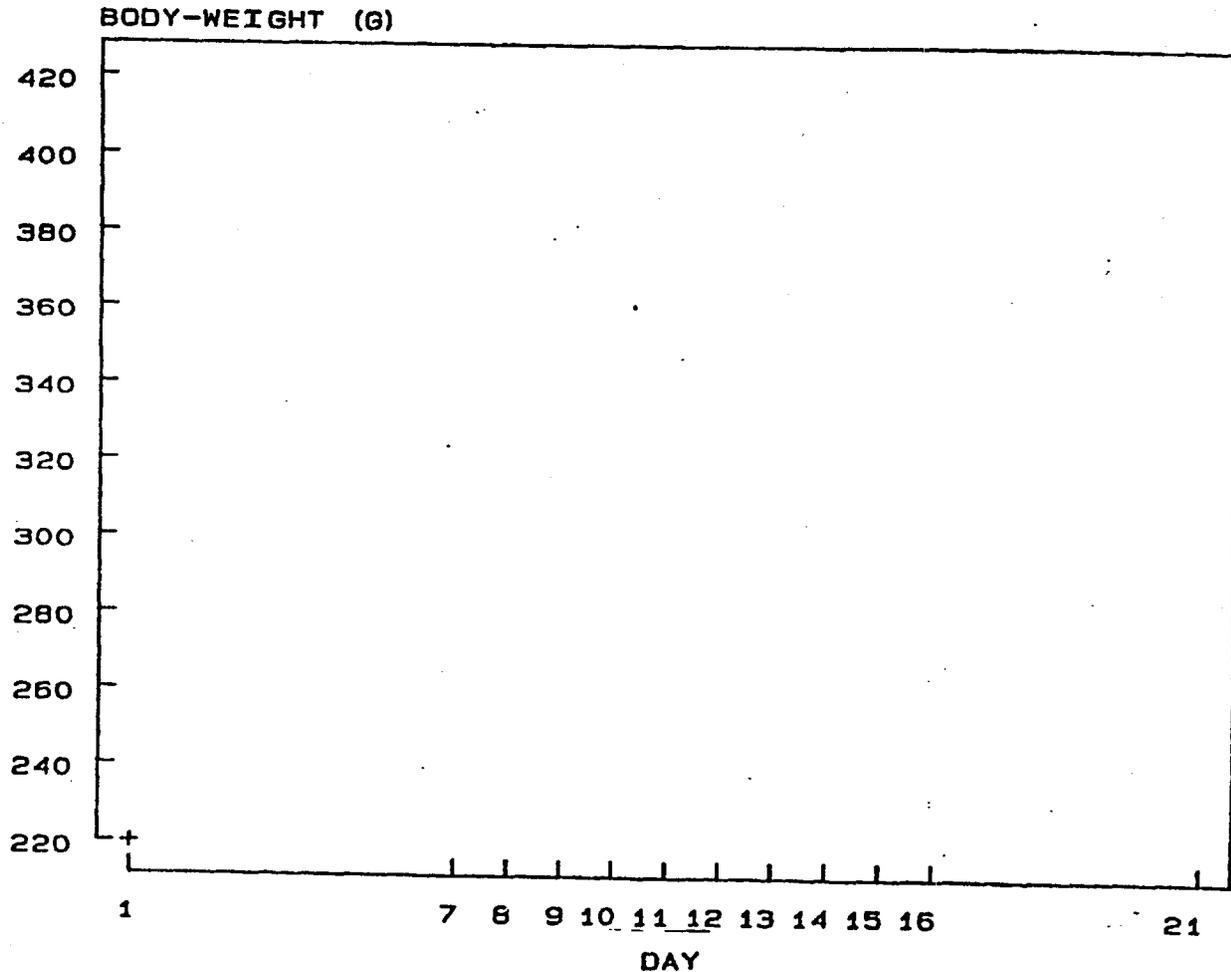


Fig. 3.2.1.1.: Average body weights of female rats ( $F_0$ ) during pregnancy. X axis: treatment in days, Y axis: weight in gm. 0: control, 1: telmisartan/HCTZ, 3.2/1.0 mg/kg/day, 2: telmisartan/HCTZ, 15.0/4.7 mg/kg/day; 3: telmisartan/HCTZ 50.0/15.6 mg/kg/day; 4: HCTZ only, 15.6 mg/kg/day

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**TABLE 3.2.1.1**  
DEVELOPMENTAL TOXICITY STUDY IN RATS: CHANGES IN BODY WEIGHT AND BODY WEIGHT GAIN

Dose (mg/kg/d)	N <sup>a</sup>	GD 8 <sup>b</sup>		GD 9		GD 12		GD 15		GD 16		GD 21	
		BW Δ%	BWG Δ%	BW Δ%	BWG Δ%	BW Δ%	BWG Δ%	BW Δ%	BWG Δ%	BW Δ%	BWG Δ%	BW Δ%	BWG Δ%
0	22		1		3		9.3		14.4		16.8		41.3
3.2/1.0	20	2.8	0.8	2.2	2.0	1.1	7.2*	1.3	12.3*	1.0	14.3*	1.1	38.6
15.0/4.7	18	0.0	0.4	-0.4	1.8*	-2.1	6.1*	-3.0	10.0*	-3.2	12.0*	-2.0	37.4
50.0/15.6	18	0.5	0.4	-0.2	1.6*	-3.2	4.6*	-4.2*	8.3*	-4.3*	10.5*	-4.0	34.2*
0/15.6	20	2.2	0.5	2.0	2.1	0.8	7.0*	1.1	12.4*	1.2	14.8	1.6	39.5

a: Excludes non-pregnant rats and one rat in the high dose combination group that had only resorptions.

b: The mean body weights of all treated groups on GD 7 (before dosing) were higher than control (3.1%, 0.8%, 1.2% and 2.9% higher for groups 3.2/1.0, 15/4.7 or 50/15.6 mg/kg/day, respectively).

\* : Significantly different from control (p<0.05)

BW: % difference in absolute body weight from concurrent control; BWG: Body weight gain as % of weight on GD 7

Food consumption was comparable between the control, low dose combination and the HCTZ alone dose groups. It was slightly but significantly lower than control (p < 0.05) for the mid (7%) and high dose (10.5%) combination groups in the first week of treatment (GDs 8-14) and remained this way in the latter group (5.5%) on GDs 15-21 (p < 0.05).

Pregnancy rates were comparable in all groups. There were no gross pathological findings in the hysterectomy groups and no significant group differences in the mean numbers of corpora lutea, implantation sites, fetuses, early and late resorptions, and mean fetal weight. No dead fetuses were found. Sex ratio was within the normal range. Preimplantation loss and resorption rate were similar in all groups. However, the only litter that was entirely resorbed was in the high dose combination group.

Administration of telmisartan in combination with HCTZ had no effect on litter and fetal parameters, though telmisartan crosses the placental barrier and is known to appear in fetal liver and fetal kidney (see section 3.5.5. of NDA #20,850). The number of dilated renal pelves found during examination of the fetal kidneys were similar in control and drug treated groups (6, 4, 1, 1 and 4 in control and the respective 4 treated groups). Malformations were observed in the control and drug treated groups. Microphthalmia and hemivertebrae in the HCTZ alone group were single and isolated findings as were brachygnathia and hydronephrosis in the high dose combination group. The sponsor considers these findings as isolated and not treatment-related.

Both AUC<sub>0-6h</sub> and C<sub>max</sub> were largely dose proportional. Table 3.2.1.2 gives the geometric rather than the conventional arithmetic mean since the data are expected to follow a log-normal rather than a normal distribution. The coadministration of telmisartan appeared to increase the C<sub>max</sub> value (but not the AUC value) of HCTZ.

**TABLE 3.2.1.2**  
**DEVELOPMENTAL TOXICITY STUDY IN RATS: TOXICOKINETICS.**  
 Measurements were made on GD 16. Geometric means of  $C_{max}$  and  $AUC_{0-6h}$  for telmisartan and HCTZ.

Dose (mg/kg/day) Telm/ HCTZ	Telmisartan		HCTZ	
	$C_{max}$ [ng/ml]	$AUC_{0-6h}$ [ng·h/ml]	$C_{max}$ [ng/ml]	$AUC_{0-6h}$ [ng·h/ml]
3.2/1.0	191	932	95	315
15.0/4.7	1210	5680	568	1830
50.0/15.6	4360	22000	1680	5760
0.0/15.6	-	-	1380	5620

**Conclusions:** Treatment with a 3.2:1 combination of telmisartan and HCTZ resulted in a slight, dose dependent decrease in body weight gain in maternal animals that did not affect reproduction capability or progeny. No teratogenic or embryotoxic potential was observed. The maternal NOAEL was below 3.2/1.0 (telmisartan/HCTZ) mg/kg/day. On the other hand, the NOAEL for developmental toxicity was 50.0/15.6 (telmisartan/HCTZ) mg/kg/day. At the latter dose,  $C_{max}$ s of telmisartan and HCTZ were 4360 and 1680 ng/ml, respectively. In normotensive women, 7 daily oral doses of 160/25 mg telmisartan/HCTZ (MRHD is 80/12.5 mg/kg/day), achieved mean telmisartan and HCTZ  $C_{max}$ s of 3190 and 193 ng/ml, respectively (study #502.114). Thus, the peak plasma levels at the no observed adverse effect dose levels of telmisartan and HCTZ for developmental toxicity were 1.4 and 8.7 times, respectively, the peak plasma levels at human dose of 160/25 mg telmisartan/HCTZ. These multiples are expected to increase when the peak plasma drug level in the rat is compared with the peak plasma level in human at the MRHD of 80/12.5 mg/kg/day (steady state data not available for the MRHD).

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#### 4. OVERALL SUMMARY AND EVALUATION

##### *Pharmacodynamics*

Telmisartan is a non-peptidic, orally-effective, potent and specific antagonist of angiotensin II, active at the AT<sub>1</sub> receptor. This action underlies the drug's efficacy for the treatment of essential hypertension (NDA 20,850). Hydrochlorothiazide (HCTZ) is a diuretic known to reduce blood pressure by eliminating water and sodium from the body. This activity, however, results in the activation of the RAS, which may offset some of the antihypertensive efficacy of the diuretic. Thus, blockade of the RAS by an angiotensin II receptor antagonist (or an ACE inhibitor) should exert a complimentary action to that of the diuretic. Therefore, a combination of an angiotensin II receptor antagonist with a thiazide diuretic is a logical approach to the treatment of hypertension. The following angiotensin II receptor antagonist/HCTZ combinations have been previously approved for the treatment of hypertension: losartan, valsartan and irbesartan.

The antihypertensive effect of telmisartan in combination with HCTZ was investigated in spontaneously hypertensive rats (SHR). Repeated oral administration of telmisartan at a dose of 3 mg/kg/day p.o. for 5 days reduced b.p. significantly and persistently with a maximal decrease in mean arterial b.p. of about 36 mm Hg after 5 days of treatment. Concomitant administration of HCTZ (10 mg/kg p.o.) with telmisartan had an even greater antihypertensive effect with a maximal reduction of mean arterial b.p. of about 53 mm Hg (60% reduction relative to baseline). The additive effect was significant compared to monotherapy. HCTZ alone had no effect on b.p. in this model. A slight but significant increase in heart rate, which was noted with the combination treatment, may have been due to reflex activation of the sympathetic nervous system.

In another study with the same model (SHR) and dosages, the sponsor investigated the effects of telmisartan and HCTZ, alone and in combination, on renal function. The study confirmed the diuretic effect of HCTZ when given alone; significant elevations in urine volume, and excretion of Na<sup>+</sup>, Cl<sup>-</sup>, K<sup>+</sup>, creatinine and glucose. The effects of the combination were more pronounced with respect to urine volume but less marked for the excretion of Na<sup>+</sup>, Cl<sup>-</sup> and K<sup>+</sup>. This suggests that the combination treatment may be beneficial in avoiding hypokalemia, a common side effect of diuretics.

##### *Pharmacokinetics*

Telmisartan, in the presence and absence of HCTZ (ratio 1:0.3), displayed similar absorption rate profiles in both rats and dogs. C<sub>max</sub> and AUC values of telmisartan did not differ significantly in the presence of HCTZ in either species. Toxicokinetic investigations in the dog suggest higher plasma C<sub>max</sub> and AUC values in females than in males. A similar trend was observed in the rat but differences did not reach a statistically significant level in either species, possibly due to high interindividual variability and a small sample size.

## *Toxicology*

### Chronic Toxicity

The potential for adverse effects following repeated oral administration of telmisartan with or without HCTZ (for 26 weeks) was investigated in the rat and the dog.

#### *Rats:*

Repeated administration of telmisartan to normotensive rats resulted in dose-dependent hypotension at doses of 4 or more mg/kg/day. This effect was potentiated by coadministration of HCTZ (ratios: 3.2:1 and 6.4:1) as evidenced by further reduced blood pressure at high doses (50/7.8 and 50/15.6 mg/kg/day). Including one control, 4 rats died or were sacrificed in moribund condition; the deaths were not attributed to drug treatment. Body weight gain (marked in males) and food consumption were significantly reduced for both sexes at 4/1.25 or more mg/kg/day. Dose-dependent significant decreases in erythrocytic parameters, prothrombin time, protein and total glycerol, and increases in BUN, creatinine (high dose groups only), potassium, magnesium and inorganic phosphate were observed in rats receiving 4/1.25 or more mg telmisartan/HCTZ/kg/day. HCTZ alone had minimal effect on hematological parameters. However, it moderately and significantly increased BUN, and decreased total protein, potassium, magnesium and inorganic phosphate. High dose combination groups (50/7.8 and 50.15.6 mg/kg/day) displayed higher values for BUN, creatinine, magnesium and inorganic phosphate than the high dose telmisartan (alone) group (50 mg/kg/day) suggesting an additive effect of HCTZ to the toxicity of telmisartan. Except for BUN, total protein and magnesium in males, all values had returned to normal within 8 weeks of termination of treatment. Hematological changes (anemia) are a class effect as it is observed with other sartans in both rats and dogs. However, thrombocytopenia and decrease in thromboplastin time is probably specific to telmisartan (with or without HCTZ) and noted only in rats. Clinically, thrombocytopenia is one of the adverse effects reported with HCTZ.

A dose-dependent decrease in heart weight was noted for telmisartan-treated males and females. The largest differences from control weight occurred in the male and female groups receiving 50/7.8 mg/kg/day (for males, about 23%; for females, about 14%, whether calculated as absolute or relative to brain weight). Statistically significant decreases from concurrent control liver, thymus and spleen weights were seen in males only. For liver, the largest effect of treatment was seen in the group receiving 50/7.8 mg/kg/day (23% absolute, 21% relative). For thymus, the difference from control was seen only in groups receiving the high dose of telmisartan, the largest effect in the group receiving 50/7.8 mg/kg/day (29% absolute, 26% relative). For spleen, the effect was seen in groups receiving any dose of telmisartan, the largest effect in the group receiving 50/7.8 mg/kg/day (15% absolute, 12% relative). HCTZ alone had no effect. Adrenal weights for male groups treated with HCTZ, alone or in combination with the high dose of telmisartan, were significantly higher than control (15% absolute, 19% relative to brain weight in the group receiving 50/7.8 mg/kg/day). For females, the opposite effect was seen (absolute and relative weights lower than control) and appeared to be associated with exposure to telmisartan, rather than HCTZ (telmisartan doses of 4 or more mg/kg/day). The largest difference from control was observed in the group receiving 50/0 mg/kg/day (14% absolute, 11% relative to brain weight) (Table 3.1.1.10).

A significant and dose-related increase (absolute and relative) in kidney weight was observed in females at doses of 4 or more mg/kg/day telmisartan, with or without HCTZ (15% absolute, 17% relative to body weight in the group receiving 50/15.6 mg/kg/day). In males, the increases (same dosage groups) were significant only on a relative to body weight basis. The largest occurred in the group receiving 50/7.8 mg/kg/day (23%). At these doses, microscopic examination of the kidney revealed arteriolar thickening, tubular atrophy, interstitial infiltration and hyperplasia/hypertrophy of the JGA apparatus. In these same groups, gastrointestinal ulceration, erosion and inflammation were observed. HCTZ had no modulating effect on the development of the JGA alterations or GI lesions. Though JGA and GI changes were reversed after compound withdrawal, arteriolar thickening and tubular atrophy persisted, as did elevated BUN (as noted above). All of the above effects had been observed previously in a 26 week study in rats receiving 4 or more mg telmisartan/kg/day (NDA #20,850).

Systemic exposure in this study was dosage-related for both telmisartan and HCTZ. Telmisartan accumulated with time (concentrations were 1.5- to 3.6-fold higher at the end of the dosing period than after the first dose). The coadministration of HCTZ did not influence the concentration of telmisartan. The no observed toxic effect dosage for adverse effects in this study was 0.1/0.03 mg telmisartan/HCTZ/kg/day. At this dose, plasma levels of HCTZ were below the limit of quantification and  $C_{max}$  and  $AUC_{0-24h}$  for telmisartan averaged 10 ng/ml and 86 ng.h/ml, respectively. In normotensive human subjects, 7 daily oral doses of 160/25 mg telmisartan/HCTZ (MRHD is 80/12.5 mg/kg/day) achieved a mean telmisartan  $C_{max,SS}$  and  $AUC_{0-24,SS}$  of 2216 ng/ml and 4834 ng.h/ml, respectively. Thus, at the no observed adverse effect level in the rat study, systemic exposure to telmisartan was 222 times lower than human exposure levels on the basis of  $C_{max}$  and 56 times lower on the basis of AUC. This NOAEL dose is, on a  $mg/m^2$  basis, only about 0.014/0.027 of the maximum recommended human dose of telmisartan/HCTZ (80/12.5 mg).

#### *Dogs:*

The chronic toxicity of telmisartan/HCTZ was evaluated in dogs at oral doses of 0.25/0.08, 1/0.31, 4/0.63, 4/1.25 and 4/0 mg/kg/day for 26 weeks. All doses resulted in significant reductions in indirect blood pressure. HCTZ (1.25 mg/kg/day) alone did not significantly affect the mean blood pressure. There were no significant changes in body weight or food consumption at any dose level. Statistically significant decreases in RBC count, hemoglobin and hematocrit were noted in all combination dose groups except the low dose group. Two high dose combination group animals were sacrificed in a moribund state with evidence of renal toxicity (cortical tubular nephropathy). Additionally, GI erosions and ulcers of the tongue and esophagus, and mineralization of the heart were seen in these two moribund animals. Evidence of similar cortical tubular dilatation, accompanied by various degrees of cortical tubule cell atrophy and degeneration, were observed in three terminal sacrifice females, two receiving 4/0.63 and one receiving 4/0 mg/kg/day of telmisartan/HCTZ. HCTZ alone was not toxic but increased the nephrotoxicity observed with telmisartan alone at the same dose level. The exaggerated pharmacological effect characterized by the development of hyperplasia/hypertrophy of the afferent arteriole in the juxtaglomerular apparatus was displayed in both sexes receiving 1.0 or more mg of telmisartan/kg/day with or without HCTZ. Statistically significant and dose-dependent increases (20 to 335% relative to control) in blood urea nitrogen were noted at dosages 1/0.31, 4/0.63, 4/1.25 and 4/0 mg/kg/day of telmisartan/HCTZ. The presence of HCTZ

appeared to exacerbate the increase in BUN, though the animals receiving HCTZ alone did not display higher BUN values. The exacerbation of nephrotoxicity could be due to increased excretion of sodium by HCTZ. However, at the dose studied (1.25 mg/kg/day), HCTZ had no effect on urinary parameters. Creatinine levels were occasionally elevated in the mid and high dose combination groups but were not statistically significantly higher than concurrent control at most time points of measurement. Relative kidney weights were slightly but significantly increased for females (only) in the higher dosage combination groups.

The concurrent administration of HCTZ did not influence the concentration of telmisartan in plasma. The no observed toxic effect dosage for the combination of telmisartan and HCTZ in this study was considered to be 0.25/0.08 mg/kg/day. At this dose, mean  $C_{max}$  and  $AUC_{0-24hr}$  of telmisartan were, respectively, 8 ng/ml and 42 ng.h/ml (male and female combined at week 26). In normotensive human subjects, 7 daily oral doses of 160/25 mg telmisartan/HCTZ (MRHD is 80/12.5 mg/kg/day) achieved a mean telmisartan  $C_{max,SS}$  and  $AUC_{0-24,SS}$  of 2216 ng/ml and 4834 ng.h/ml, respectively. Thus, at the no observed adverse effect level in the dog study, systemic exposure to telmisartan was 277 times lower than human exposure levels on the basis of  $C_{max}$  and 115 times lower on the basis of AUC. The NOAEL dose of 0.25/0.08 mg telmisartan/HCTZ/kg/day is, on a  $mg/m^2$  basis, only about 0.1/0.2 of the maximum recommended human dose of telmisartan/HCTZ (80/12.5 mg).

In a previously conducted 52 week dog study with telmisartan alone, the no observed adverse effect dose was higher, 5 mg/kg/day (NDA #20850). The reason for the difference, the sponsor contends, lies with the different strain of beagle dog used. However, addition of HCTZ may have potentiated the toxic effects of telmisartan, resulting in a lowering of the NOAEL.

#### Genotoxicity

There were no genetic toxicology studies performed with the combination.

#### Reprotoxicity

A developmental toxicity study with telmisartan and HCTZ was conducted in rats at telmisartan/HCTZ doses of 3.2/1.0, 15.0/4.7, 50.0/15.6 and 0/15.6 mg/kg/day given on gestation days 7 through 16. The combination had no effect on litter or fetal parameters, though a previous study with telmisartan alone had shown it to cross the placental barrier and appear in fetal liver and kidney (NDA #20,850). As with telmisartan monotherapy, a significant and dose-dependent decrease in maternal body weight gain was noted for all dose groups. The NOAEL for developmental toxicity was 50.0/15.6 (telmisartan/HCTZ) mg/kg/day. Pregnancy did not alter the pharmacokinetic profile of telmisartan in rats. Maternal  $C_{max}$  and AUC values obtained in pregnant animals were not remarkably different from values obtained over a similar dose range in non-pregnant rats in general toxicity studies. At the NOAEL for developmental toxicity,  $C_{max}$ s of telmisartan and HCTZ were 4360 and 1680 ng/ml, respectively. In normotensive women, 7 daily oral doses of 160/25 mg telmisartan/HCTZ (MRHD is 80/12.5 mg/kg/day), achieved mean telmisartan and HCTZ  $C_{max}$ s of 3190 and 193 ng/ml, respectively. Thus, the peak plasma levels at the no observed adverse effect dose levels of telmisartan and HCTZ for developmental toxicity were 1.4 and 8.7 times the peak plasma levels at the dose of 160/25 mg telmisartan/HCTZ in

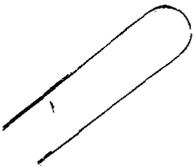
women. These multiples are expected to increase when the NOAEL for developmental toxicity in the rat is compared with the MRHD (steady state data not available for the MRHD). Rat and human AUCs were not compared as plasma drug levels were measured for only 6 hr in the pregnant rat *versus* 24 hr for women. When compared on a mg/m<sup>2</sup> basis, the rat NOAELs are about 7 and 14 times the MRHD of telmisartan and HCTZ, respectively.

## 5. LABELING

Those sections of the proposed labeling (version 12/13/99) that refer to preclinical studies were reviewed and the following changes are recommended:

[ Draft Labeling ]

REDACTED



A similar correction is needed for telmisartan (MICARDIS<sup>®</sup>) tablets (original NDA 20,850).

**6. RECOMMENDATIONS**

This new drug application for telmisartan/HCTZ is approvable with recommended changes in labeling (see page 52).

[ *ISI* ]  
G. Jagadeesh, Ph.D.

cc:  
Original NDA 21,162 (Telmisartan/HCTZ)  
HFD-110  
HFD-110/CSO  
HFD-345/  
Accepted by CA/R on 6-13-00

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