CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 21-162

PHARMACOLOGY REVIEW(S)

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NDA #21,162

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REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA

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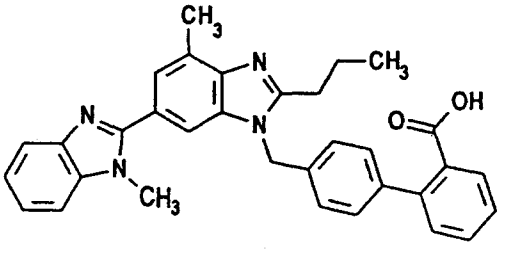
SPONSOR Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Road
PO Box 368
Ridgefield, CT 06877

DRUG PRODUCT Telmisartan/HCTZ Tablets

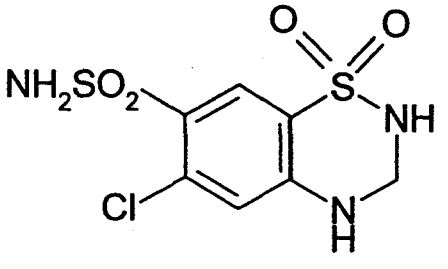
DRUG CHEMISTRY

Telmisartan
Code Names: BIBR0277SE, BIBR 277 SE
Chemical Name: 4'-[(1,4'-dimethyl-2'-propyl[2,6'-bi-1H-benzimidazol]-1'-yl)methyl]-[1,1'-biphenyl]-2-carboxylic acid.
CAS Registry No.: 144701-48-4



M.W. 514.63

Hydrochlorothiazide
Code Names: None
Chemical Name: 2H-1,2,4-benzothiadiazine-7sulfonamide,6-chloro-3,4-dihydro-1,1-dioxide
CAS Registry No.: 58-93-5



M.W. 297.74

PHARMACOLOGICAL CLASS Telmisartan: Angiotensin II receptor antagonist
HCTZ: Diuretic

INDICATION Treatment of hypertension

FORMULATION Telmisartan/HCTZ tablets for oral administration contain 40 or 80 mg of telmisartan and 12.5 mg HCTZ. Inactive ingredients in the tablet are povidone, sodium hydroxide, meglumine, sorbitol, magnesium stearate, lactose monohydrate, microcrystalline cellulose, corn starch, iron oxide red and sodium starch glycolate.

PROPOSED DOSAGE REGIMEN A patient whose blood pressure is inadequately controlled with 80 mg telmisartan monotherapy may be switched to the fixed combination of 80 mg telmisartan/12.5 mg HCTZ once daily. A patient whose blood pressure is inadequately controlled by 25 mg hydrochlorothiazide, or experiences hypokalemia with this regimen, may be switched to the combination of 40 mg telmisartan/12.5 mg hydrochlorothiazide once daily (reducing the dose of HCTZ without reducing the overall expected antihypertensive response). If b.p. remains uncontrolled after 2-4 weeks of therapy, the dose may be titrated up to the 80/12.5 mg combination.

[redacted] **UNDER WHICH CLINICAL TRIALS WERE CONDUCTED** [redacted]

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INTRODUCTION

The renin-angiotensin-aldosterone system (RAAS) plays a central role in blood pressure homeostasis and is involved in the pathogenesis of various forms of hypertension. The RAAS is a dual hormone system, serving as both a circulating and a local tissue hormone system (i.e., local mediator) as well as neurotransmitter or neuromediator functions in the CNS. Control of blood pressure by the RAAS is exerted through multiple actions of angiotensin II, a small peptide which is a potent vasoconstrictor hormone implicated in the genesis and maintenance of hypertension. Hypertension is a primary risk factor associated with cardiovascular, cerebral and renal vascular disease. One of the approaches to the treatment of hypertension, which may be considered as a major scientific advancement, involves the use of drugs affecting the RAAS. Pharmacological interruption of the RAAS was initially employed in the late 1970s with the advent of the angiotensin converting enzyme (ACE) inhibitor, captopril. ACE inhibitors have since gained widespread use in the treatment of mild to moderate hypertension, congestive heart failure, myocardial infarction, and diabetic nephropathy. Although ACE inhibitors are well tolerated, they are also involved in the activation of bradykinin, enkephalins, and other biologically active peptides. These actions result in adverse effects such as cough, increased bronchial reactivity, and angioedema. Thus, the goal of achieving a more specific blockade of the effects of angiotensin II than is possible with ACE inhibition. The introduction of the nonpeptide angiotensin II receptor antagonist losartan in 1995 marked the achievement of this objective and has opened new vistas in understanding and controlling the additional biological effects of angiotensin II. Since then there has been an explosive growth in the amount of research being done to discover orally active nonpeptide angiotensin II receptor antagonists.

Telmisartan, an orally active AT_1 selective angiotensin II receptor antagonist originating from Boehringer Ingelheim Pharmaceuticals, Germany, was approved for the treatment of hypertension in late 1998 (NDA 20,850). Hydrochlorothiazide (HCTZ) is a diuretic first approved for the treatment of hypertension in mid 1958. It affects the distal renal tubular mechanism of electrolyte reabsorption and increases excretion of sodium and chloride in approximately equivalent amounts. It is widely used alone or in combination with other antihypertensive agents including ACE inhibitors (e.g., captopril) and AT_1 receptor antagonists (e.g., losartan, irbesartan, and valsartan). The increase in sodium and fluid excretion during administration of the diuretic agent leads to a reflex activation of the RAAS characterized by a significant increase in plasma renin and angiotensin. Therefore, the addition of any drug that blocks the RAAS would be expected to cause a potentiation of the antihypertensive effects of the diuretic, HCTZ. It is believed that the fixed combination provides potential benefits in terms of efficacy, compliance, and convenience to appropriate patients.

This review summarizes the sponsor's preclinical evaluation of telmisartan in combination with HCTZ.

1. PHARMACODYNAMICS

1.1. Effects of Repeated Oral Administration of Telmisartan and HCTZ, Alone and in Combination, on Blood Pressure and Heart Rate in Spontaneously Hypertensive Rats (SHR) (Study #w110396, Doc #U96-2175)

Telmisartan alone at doses 0.3 or more mg/kg p.o. given for 4 days reduced both systolic and diastolic blood pressures in rats with renovascular (high renin) hypertension and in genetically hypertensive rats (SHR) (NDA #20,850). This study investigated whether the combined administration of telmisartan and HCTZ results in additive antihypertensive effect in SHR compared to telmisartan mono-treatment.

Male spontaneously hypertensive rats (SHR; Charles River, weight approximately 300 g) were anesthetized with pentobarbital sodium (50 mg/kg i.p.) and were chronically instrumented with pressure transducers. The animals were allowed to recover for several weeks and housed individually in cages. Animals were not fasted overnight prior to the administration of compounds. Telmisartan (lot #8350081) at 3 mg/kg and HCTZ (lot #H4759) at 10 mg/kg either alone or in combination were given orally by a gastric tube (2 ml/kg body weight) once daily for 5 days (n=10/dose level). Blood pressure and heart rate were monitored in conscious state continuously during treatment and for up to 10 days after treatment. The compounds were prepared in 0.5% aqueous Natrosol® (hydroxyethylcellulose) as suspensions.

Results

Vehicle and HCTZ (10 mg/kg) had negligible effects on diastolic, systolic and mean blood pressures and heart rate during the 15 days observation period. Telmisartan alone reduced both components of b.p. significantly ($p < 0.05$) and persistently from the first day of administration (Fig. 1.1.1). The reduction in blood pressure was time-dependent with peak effect measured after 5 days of treatment. Blood pressure returned gradually to predrug values after cessation of treatment (Table 1.1.1). No rebound hypertension was observed.

Concomitant administration of HCTZ with telmisartan had a greater antihypertensive effect than that observed with telmisartan alone ($p < 0.05$, Fig. 1.1.1).

The changes in heart rate in the telmisartan- and HCTZ-treated groups were not significantly different from the vehicle treated group. A moderate (approx. + 20 beats/min), yet significant increase ($p < 0.05$) in heart rate as compared to the vehicle treated group was observed in the group with combination treatment. The rise in heart rate could be due to over proportional reflex activation of the sympathetic nervous system. After cessation of treatment, this increase in heart rate was no longer evident.

In conclusion, the study demonstrated that the combination of telmisartan with HCTZ results in a significant additive antihypertensive effect when compared with monotherapy.

TABLE 1.1.1

EFFECTS OF TELMISARTAN (3 MG/KG) AND THE COMBINATION OF TELMISARTAN AND HCTZ (3 + 10 MG/KG), ADMINISTERED ORALLY FOR 5 DAYS, ON DIASTOLIC, SYSTOLIC AND MEAN BLOOD PRESSURES IN CONSCIOUS SHR.

Values Given are Mean Changes (mm Hg) From Baseline (day 0.0).

Day	Diastolic b.p.		Systolic b.p.		Mean b.p.	
	Telmisartan	Telm./hctz	Telmisartan	Telm/hctz	Telmisartan	Telm/hctz
0.0	0.00	0.00	0.00	0.00	0.00	0.00
1.0	-19.00	-26.00	-19.00	-26.00	-19.00	-30.00
2.0	-22.00	-35.00	-22.00	-35.00	-26.00	-41.00
3.0	-26.00	-38.00	-26.00	-38.00	-30.00	-46.00
4.0	-29.00	-40.00	-29.00	-40.00	-34.00	-48.00
5.0	-31.00	-44.00	-31.00	-44.00	-36.00	-53.00
6.0*	-22.00	-25.00	-22.00	-25.00	-26.00	-34.00
8.0*	-11.00	-15.00	-11.00	-15.00	-14.00	-21.00
15.0*	-3.00	-5.00	-3.00	-5.00	-6.00	-7.00

* No treatment

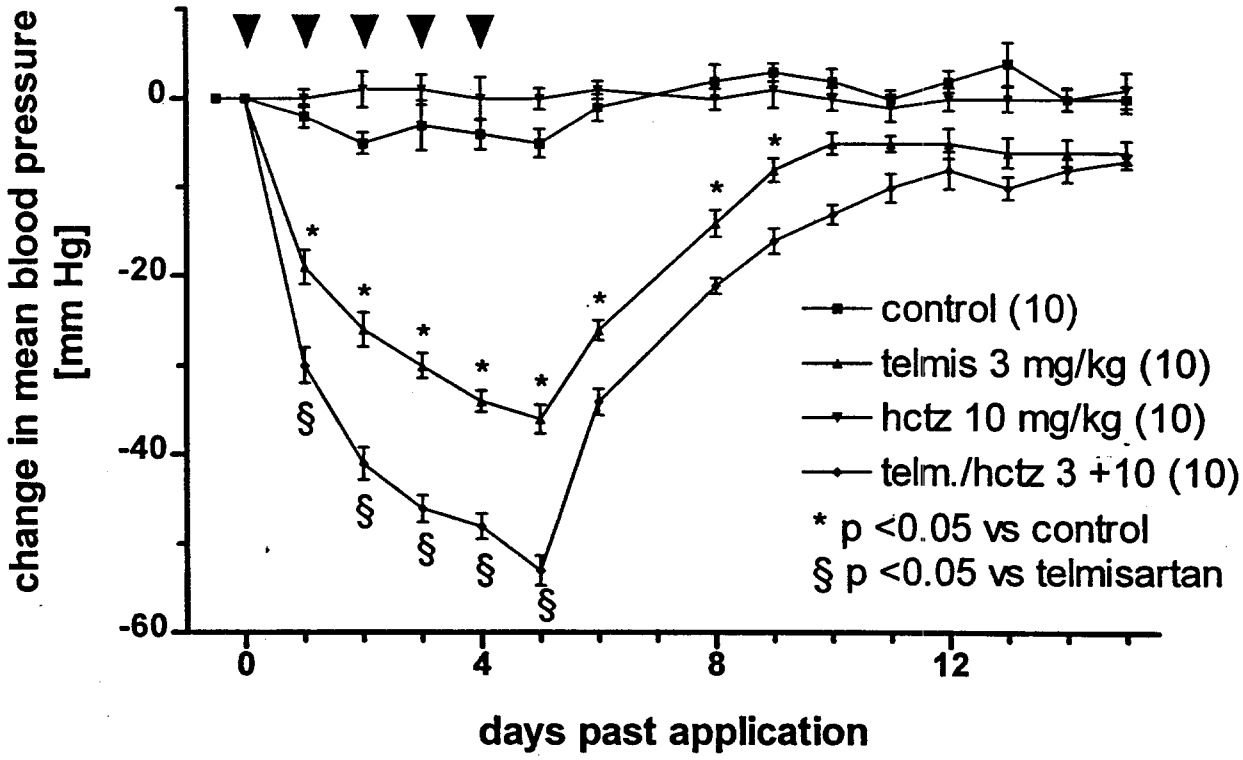

Fig. 1.1.1.: Effects of vehicle, telmisartan, HCTZ and the combination of telmisartan and HCTZ on mean blood pressure in conscious, spontaneously hypertensive rats. Values are the mean ± SE. The number of animals in each group is indicated in brackets. *: statistically significant *vs* vehicle treated group by Dunnett's test. §: statistically significant *vs* telmisartan alone by Tukey-Kramer's test.

1.2. Effects of Repeated Oral Administration of Telmisartan and HCTZ, Alone and in Combination, on Renal Function and Blood Pressure in Spontaneously Hypertensive Rats (SHR) (Study #GP95-127-HS, Doc #U96-2186)

The aim of the study was to investigate the effects of telmisartan and HCTZ, alone and in combination, on renal function and blood pressure in SHR after repeated oral administration.

Male spontaneously hypertensive rats (SHR; _ weighing 380 to 430 g) received the vehicle (0.5% aqueous Natrosol®) or drug (telmisartan 3 mg/kg, HCTZ 10 mg/kg, or combination of telmisartan and HCTZ 3.0/10.0 mg/kg) orally (2 ml/kg body weight) once daily for 5 days (n=18/dose level). The drug solutions were prepared as described in the previous section. Urine from 9 animals in each group and blood samples from the remaining 9 animals in each group were collected on day -1 (pre treatment), day 5 (after 5 days treatment) and day 14 (9 days after the last administration) at 4, 8 and 24 hours after the administration of the compounds or the vehicle. Urine volume and pH, as well as the concentrations of Na^+, Cl^-, K^+, creatinine, glucose and protein, were determined. The same parameters were assessed in serum samples, with the exception that BUN was measured instead of protein. The systolic arterial blood pressure was indirectly determined at the same time points according to the method of RIVA-ROCCI with the help of a sphygmomanometer cuff around the tail of the immobilized rat.

Results

Administration of telmisartan and HCTZ, either alone or in combination, did not change the parameters measured in serum at the different time points with the exception of BUN. BUN was significantly elevated ($p < 0.01$) after 8 and 24 hr on day 5 of treatment in groups receiving HCTZ, alone (16% relative to day –1) or in combination with telmisartan (10% relative to day –1).

Telmisartan did not cause significant changes in any of the measured urine parameters. HCTZ induced significant elevations in urine volume, Na^+, Cl^-, K^+, creatinine and glucose for the collecting periods 0-4 h, 4-8 h and for the complete sampling period (0-24 h). The effects of the combination relative to vehicle control were more pronounced with respect to urine volume and less marked for the excretion of Na^+, Cl^-, K^+ ($p < 0.01$) (Table 1.2.1). Both creatinine and glucose remained unchanged after the administration of the combination of telmisartan and HCTZ.

TABLE 1.2.1

EFFECTS OF TELMISARTAN (3 MG/KG), HCTZ (10 MG/KG) AND THE COMBINATION (3 + 10 MG/KG), ADMINISTERED ORALLY, ON URINE PARAMETERS IN SHR.

Measurements were made 4, 8 and 24 hours after the administration of the compound or its vehicle on day –1, day 5 and day 14 (not shown). Data are presented as Mean ± SD, N=8-9.

Parameter	vehicle		Telmisartan		HCTZ		Telmisartan/HCTZ	
	day –1	day 5	day –1	day 5	day –1	day 5	day –1	day 5
Volume (ml/100g)								
T0-4h	1.43±0.39	1.66±0.20	1.77±0.59	1.85±0.37	1.42±0.93	2.64±0.53 *	1.78±0.49	2.77±0.55 *
T4-8h	0.83±0.44	1.05±0.85	1.23±0.76	0.72±0.23	1.52±0.76	1.06±0.38	1.08±0.74	1.17±0.74
T8-24h	1.92±1.01	2.28±1.29	2.71±1.37	3.21±1.46	2.58±1.44	2.97±1.05	2.17±1.18	4.26±1.72
T0-24h	**4.18±1.31**	**4.99±2.08**	**5.71±2.09**	**5.78±1.67**	**5.51±2.30**	**6.67±0.92**	**5.03±1.95**	**8.20±2.13 ***
Na^+ (µmol/100g)								
T0-4h	10.34±9.06	10.14±2.70	9.97±3.32	17.82±8.66	13.04±12.27	152.10±45.44 *	8.90±2.48	99.72±48.72 *
T4-8h	8.96±10.46	17.48±11.61	15.03±16.44	23.35±15.47	11.33±6.99	56.58±25.29 *	9.81±10.24	38.22±26.80
T8-24h	102.27±60.25	84.81±40.15	96.50±43.49	67.27±16.57	71.52±35.32	53.73±24.15	72.58±28.10	48.78±17.07
T0-24h	**121.57±76.05**	**112.43±42.36**	**121.50±56.40**	**108.43±33.00**	**93.00±36.81**	**262.41±64.38***	**91.28±29.48**	**182.48±59.40**
K^+ (µmol/100g)								
T0-4h	62.30±24.67	103.76±23.47	64.76±29.55	123.65±28.02	74.21±29.20	212.12±24.96 *	60.85±17.16	192.22±26.91 *
T4-8h	58.28±16.71	62.11±22.42	62.41±18.37	63.55±21.92	79.24±70.88	63.67±13.00	58.41±22.60	67.04±26.19
T8-24h	118.16±39.21	165.48±28.36	119.27±22.36	182.05±20.93	112.33±26.83	146.22±27.55	106.66±18.18	137.09±24.50
T0-24h	**238.74±49.49**	**331.34±41.60**	**246.43±43.41**	**369.25±41.39**	**249.29±59.02**	**422.01±43.60 ***	**225.92±34.67**	**396.00±64.27**
Cl^- (µmol/100g)								
T0-4h	19.59±12.38	27.90±10.84	23.32±10.00	38.05±9.95	28.65±22.08	228.85±42.18 *	19.34±7.14	149.60±47.82 *
T4-8h	10.56±4.49	12.06±8.57	17.19±11.32	16.49±11.80	26.37±24.95	39.74±19.12 *	13.38±7.73	32.93±19.65
T8-24h	52.73±27.45	37.15±19.37	55.23±10.92	53.55±11.53	54.01±22.15	29.90±10.31	43.98±7.76	46.05±13.96
T0-24h	**82.88±41.94**	**77.11±28.44**	**95.74±25.36**	**108.09±21.74**	**102.66±35.51**	**298.50±51.84 ***	**76.69±15.41**	**228.59±70.33 ***
creatinine (µmol/100g)								
T0-4h	3.87±0.71	4.36±0.59	4.06±0.94	4.75±0.84	4.48±0.99	5.83±0.79 *	4.29±1.04	5.26±0.53
T4-8h	5.18±1.63	4.93±1.73	4.97±1.35	4.79±1.43	5.15±2.70	4.99±1.12	4.49±1.50	5.02±1.94
T8-24h	16.68±3.47	17.95±2.35	16.79±1.00	18.40±1.44	15.90±2.74	17.78±0.96	15.98±2.11	18.73±1.35
T0-24h	**25.74±3.68**	**27.24±2.12**	**25.83±1.94**	**27.94±2.00**	**24.53±2.69**	**28.61±1.56**	**24.76±2.88**	**29.02±2.78**
glucose (µmol/100g)								
T0-4h	0.81±0.22	1.07±0.18	0.82±0.26	1.17±0.30	1.02±0.33	1.50±0.25 *	0.84±0.26	1.31±0.24
T4-8h	0.85±0.25	0.93±0.29	0.84±0.28	1.00±0.33	0.98±0.69	0.95±0.20	0.73±0.25	0.91±0.38
T8-24h	2.06±0.43	2.26±0.40	2.00±0.19	2.29±0.35	2.02±0.62	2.11±0.29	2.03±0.35	1.91±0.21
T0-24h	**3.73±0.55**	**4.26±0.29**	**3.66±0.58**	**4.46±0.50**	**3.79±0.84**	**4.56±0.31**	**3.60±0.52**	**4.12±0.56**

*: $p<0.01$ *vs* control

Systolic blood pressure was significantly reduced compared to control in all treated groups. The reduction on day 5 of treatment was 21, 34 and 47 mm Hg in animals receiving HCTZ, telmisartan and the combination, respectively (Table 1.2.2), demonstrating the additive effect of telmisartan when administered in combination with HCTZ.

TABLE 1.2.2
EFFECTS OF TELMISARTAN (3 MG/KG), HCTZ (10 MG/KG) AND THE COMBINATION (3 + 10 MG/KG), ADMINISTERED ORALLY, ON BLOOD PRESSURE IN SHR.

Measurements were made on day –1, day 5 and day 14. Data are presented as Mean ± SD, N=8-9.

Treatment	Syst. Blood Pressure	% of pre treatment	reduction mm/Hg *vs* control at day 5
Control			
pre treatment	197.9 ± 3.1		
day 5	188.6 ± 5.7	95.4 ± 3.2	0
day 14	178.9 ± 2.4	90.5 ± 1.4	
Telmisartan 3mg/kg p.o.			
pre treatment	203.8 ± 3.8		
day 5	154.9 ± 5.3 *	76.1 ± 2.6 *	- 34
day 14	179.3 ± 4.0	88.2 ± 2.1	
HCTZ 10 mg/kg p.o.			
pre treatment	198.9 ± 3.3		
day 5	167.6 ± 4.2 *	84.5 ± 2.8 *	- 21
day 14	179.9 ± 3.3	90.6 ± 2.2	
Telm/HCTZ 10/3 mg/kg p.o.			
pre treatment	204.6 ± 2.4		
day 5	141.2 ± 3.0 *	69.1 ± 1.8 *	- 47
day 14	184.9 ± 4.1	90.4 ± 2.2	

*: $p<0.01$ vs control

2. DRUG DISPOSITION (ADME)

2.1. Pharmacokinetics of Telmisartan and HCTZ in Rats (Study #B1154, Doc. #U99-1283). Vol. 11

This non-GLP study was conducted by the department of Pharmacokinetics and Drug Metabolism at Boehringer Ingelheim, D-88397 Biberach, Germany (study dates not given, date of report, March 17, 1999). The objective of the study was to determine whether the combination of the two drugs has any influence on their pharmacokinetics.

Male albino rats (Chbb:THOM, Wistar, SPF) weighed 259 to 273 gm (age not given) at the start of the study. Suspensions of telmisartan and HCTZ, alone or in combination in 0.5% Natrosol, were administered orally by gavage. Animals received a single 3 mg/kg dose of telmisartan in combination with a 10 mg/kg dose of HCTZ or received telmisartan or HCTZ alone, at a dose of 3 or 10 mg/kg, respectively (n=5/dose). The animals were fasted for about 16 hr before the start of the study and provided food 2 hr after dosing. Blood samples were collected, under anesthesia, by puncturing the orbital venous sinus at 1, 2, 4, 8 and 24 hr following administration.

Results

After oral administration of telmisartan, alone or in combination with HCTZ, T_{max} ranged between 2 and 8 hr with a mean of 5.2 and 3.6 hr, respectively. C_{max} values for telmisartan did not differ significantly, suggesting no interaction in the pharmacokinetics of telmisartan in the presence of HCTZ. The AUC for telmisartan administered alone (1059 ng.hr/ml) was slightly less than when administered in combination with HCTZ (1379 ng.h/ml). However, the values were not significantly different (due to large standard deviation). In contrast, the terminal elimination half-life ($t_{½}$) of telmisartan was prolonged in the presence of HCTZ relative to monotherapy (Table 2.1.1).

The course and shape of the plasma concentration-time curves for HCTZ after administration of 10 mg/kg HCTZ alone or in combination with telmisartan were similar. C_{max}, T_{max} and AUC values were comparable for both groups (Table 2.1.1).

The sponsor concludes that no drug interaction in the pharmacokinetics of telmisartan or HCTZ was observed in rats following a single dose of the combination in comparison to the monotherapy. However, they fail to address the increase in the terminal elimination half-life of telmisartan (from 5.35 to 10.5 hr) in the presence of HCTZ.

TABLE 2.1.1
PHARMACOKINETIC PARAMETERS OF TELMISARTAN (3 MG/KG) AND HCTZ (10 MG/KG) IN RATS GIVEN ALONE OR IN COMBINATION

	Measured substance: Telmisartan		Measured substance: HCTZ	
Parameter	Telmisartan alone	Telmisartan + HCTZ	HCTZ alone	HCTZ + Telmisartan
C_{max} [ng/ml]	94.71	113.00	1259.00	1239.00
T_{max} [hour]	5.20	3.60	1.80	1.60
$t_{½}$ [hour]	5.35	10.50	3.78	4.91
AUC_{0-24} [ng·h/ml]	1069.00	1389.00	3933.00	3604.00
Cl [ml/min/kg]	44.91	28.74	42.37	45.66

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2.2. Pharmacokinetics of Telmisartan and HCTZ in Dogs (Study #B1157, Doc. #U99-1341). Vol. 11

This non GLP study was conducted by the department of Pharmacokinetics and Drug Metabolism at Boehringer Ingelheim, D-88397 Biberach, Germany, between January 16 and February 7, 1996 (study dates not given; date of report, April 6, 1999). The objective of the study was to determine whether the combination of the two drugs has any influence on their pharmacokinetics.

Male and female beagle dogs weighed 11.6-13.4 kg (age not given) at the start of the study. Telmisartan and HCTZ were suspended in 0.5% Natrosol and administered orally by gavage at a dose of 1/0.3 mg/kg. Animals also received HCTZ alone at a dose of 0.3 mg/kg (n=2/sex). For data on the pharmacokinetics of telmisartan administered alone, a previously reviewed study (study #B97, Doc. #U92-0600. reviewed under NDA 20,850 section 2.1.6) was selected. In the latter study, 2 male and 2 female dogs each received single oral doses of 1 mg [^{14}C]telmisartan/kg by gavage. In both studies, the animals were fasted (for at least 12 hr) before the start of the study and provided food 2 hr after dosing. Blood samples were collected from the antebrachic vein at 0, 1, 2, 4, 7 and 24 hr following administration of the combination or HCTZ (study #B1157), and 0, 0.5, 1, 2, 4, 6, 8, 24, 32 and 48 hr following administration of telmisartan (study #B97).

Results

Plasma levels of telmisartan, administered alone or in combination with HCTZ, were highly variable (CV >50%). With telmisartan administered alone, C_{max} varied from 12.2 to 110.1 ng/ml (geometric mean 39.2), and when administered in combination with HCTZ, the values varied from 118.6 to 319.5 ng/ml (gmean = 177.9). The mean plasma concentrations 24 hr after administration were 4.7 and 10.4 ng/ml, respectively, for the telmisartan alone and combination groups. In agreement with this, the $AUC_{0\text{-}24hr}$ value for the combination group (990 ng.hr/ml) was much higher than for the telmisartan alone group (267 ng.hr/ml) (Table 2.2.1). The results suggest an interaction of these drugs in dogs. But the sponsor disagrees and suggests that the difference in AUCs was due to an extreme variability in values caused by a difference in the state of nutrition, which can influence the absorption and the glucuronidation of the drug. The sponsor compares the current results for the combination group to the results of a 26-week toxicity study in dogs (study #U99-3058, section 3.1.2), which also registered a high variation in plasma levels after both treatments. An examination of the values (both C_{max} and AUC) in that study (see Table 3.1.2.10) suggests an absence of any effect of HCTZ on the pharmacokinetics of telmisartan.

In contrast to the above findings, the plasma concentration/time profiles of HCTZ measured in both mono and combination therapy were comparable (Table 2.2.1).

TABLE 2.2.1
PHARMACOKINETIC PARAMETERS AFTER SINGLE ORAL ADMINISTRATION OF TELMISARTAN (1 MG/KG) AND HCTZ (0.3 MG/KG) TO DOGS, GIVEN ALONE OR IN COMBINATION.

Data are arithmetic means of 2 male and 2 female dogs; range is shown in parentheses

Parameter	Measured substance: Telmisartan			Measured substance: HCTZ		
	Telmisartan + HCTZ		Telmisartan alone, study #U92-0600[b]	HCTZ + Telmisartan		HCTZ alone, present study
	Present study	Study #U99-3058[a]		Present study	Study #U99-3058[a]	
C_{max} [ng/ml]	192.5 (118.6 - 319.5)	50.0	51.7 (12.2 - 110.1)	72.06	121.0	81.76
T_{max} [hour]	2.75 (1.0 - 4.0)		7.50 (2 - 24)	1.25		1.50
$t_{½}$ [hour]	7.81 (4.1 - 13.0)		4.6 (4.1 - 15.1)	2.03		3.59
AUC_{0-24} [ng·h/ml]	989.90 (614 - 1465)	337.0 (178 - 646)	267.3 (155.3 - 407.8)	239.40*	443.3 (245 - 665)	244.60*
Cl [ml/min/kg]	16.84 (10.3 - 24.4)		57.13 (39.6 - 76.2)	19.35		17.05

a: see section 3.1.2 for details; values taken on study day 1 at dose of 1/0.31 mg/kg/day telmisartan/hydrochlorothiazide

* plasma levels were below quantifiable level at 24 hr; thus AUC was calculated up to 7 hr

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3. TOXICOLOGY

3.1. *Chronic Toxicity*

3.1.1. 26-Week Oral Toxicity Study of Telmisartan/HCTZ in Rats (Study #96B027, Doc. #U99-1556) Vol. 11-16

This GLP study was conducted by the department of experimental pathology and toxicology at Boehringer Ingelheim, D-88397 Biberach an deer Riss, Germany, between March 20 and November 12, 1996. The objective of the study was to assess the potential toxicity of a drug combination when given daily at a graduated dose levels over a period of 26 weeks. Also, the study was to investigate if HCTZ has a modulating effect on the toxicity resulting from telmisartan.

Animals: Male and female albino rats (Chbb:Thom, (SPF))
Age at study start: 73 days
Weight at study start: Males: 283.2-362.7 gm, Females: 168.1-242.1 gm

Test substances, telmisartan (batch #8550141) and HCTZ (batch #150788/924950), alone or in combination (ratios, 3.2 and 6.4), were 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. Drugs were given each day in the morning, using a tuberculin syringe and stomach tube, for 26 weeks, 7 days a week. No drug was given during an 8-week recovery phase. The animals were housed in groups of 5. The study design was as follows.

Group #	Substance	Dose mg/kg/d	Main study*				Toxicokinetic study	
			Regular		Recovery			
			M	F	M	F	M	F
G 0	Natrosol	10 ml/kg	20	20	10	10	4	4
G 1	Telmisartan/HCTZ	0.1/0.03	20	20			4	4
G 2	Telmisartan/HCTZ	4/1.25	20	20			4	4
G 3	Telmisartan/HCTZ	50/7.8	20	20			4	4
G 4	Telmisartan/HCTZ	50/15.6	20	20	10	10	4	4
G 5	Telmisartan	50	20	20			4	4
G 6	HCTZ	15.6	20	20			4	4

*Additionally, 5 male and 5 female animals were provided for microbiological examinations. The examinations were carried out in 1 male and 1 female in study weeks 2, 14, 26 and 35.

The doses were selected on the basis of a 9-week oral administration study in which telmisartan/HCTZ caused a reduction in body weight gain at all dose levels (9.7, 12.2 and 15.8% at doses of 3.2/1, 48/7.5 and 96/15 mg/kg/day, respectively) corresponding to reduced food consumption (6 to 16.7%). Systolic blood pressure was reduced, dose-dependently, for more than 24 hr. At the low dose (3.2/1 mg/kg/day), the following changes considered of toxicological importance were noted: reduced RBC count (females only), reduced hematocrit and total protein concentration (both sexes), elevated potassium (only in females), elevated total glycerol (only in males) and elevated BUN (both sexes). Histopathological examination revealed only marginal

changes compared to controls. At mid and high doses, all the above parameters were more pronounced in both sexes. In addition, reduced thromboplastin time and decreased albumin concentration and increased concentration of total cholesterol (males only), creatinine and magnesium were noted. Histopathological examination revealed gastric mucosal injury, consisting of erosions and ulcers of the mucosa of the glandular stomach, in all animals given mid and high doses. Pharmacologically-mediated juxtaglomerular cell hyperplasia was observed in drug-treated animals at all doses, and JGA hypertrophy and vacuolation were observed at the mid and high doses. Slight acute tubular generation was observed in kidneys of 2 of 5 high dose males and mild single cell necrosis with regenerative hyperplasia was observed in a third. This led the sponsor to set the low dose for the 26-week study to 0.1/0.03 and the high dose to 50/15.6 mg/kg of telmisartan/HCTZ. The high dose was tested at telmisartan/HCTZ dose ratios of 3.2:1 and 6.4:1, both of which are intended for clinical development.

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.
Blood Pressure (tail cuff method) and Heart Rate (n=4 M, 4 F/dose group): study weeks 5, 13, 25 and 33 (recovery period groups) at 0, 2 and 5 hr after drug administration.
Hematology and Clinical Chemistry: weeks 4, 13/14, 25/26 and 33/34 (recovery groups only).
Urinalysis: weeks 4, 13/14, 24 and 33 (recovery groups only).
Feces Examined for Occult Blood: weeks 4, 25 and 34 (recovery groups only).
Plasma Telmisartan and HCTZ: study days 1 at 0, 1, 2, 4, 7 and 24 hr postdose; 85 at 0, 2 and 7 hr postdose; 181 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.

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

* Organ weighed (relative organ weights were calculated in relation to body or brain weight)

Eyes were fixed in Davidson solution and 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 combination groups were microscopically examined. Tissues from lower dosage groups and monotherapy groups (G5, G6) were microscopically examined only if macroscopic changes had been observed or they had been designated target organs on the basis of findings in the high dose combination group.

Results

A total of 4 rats (including one female from the toxicokinetics group) died or were sacrificed for humane reasons during the study (Table 3.1.1.1). No animal from any combination group died. Based on the histopathology examinations, the sponsor considers all deaths were unrelated to drug treatment. However, the high dose female demonstrated liver necrosis and mucosal erosions in the stomach, which could be attributed to treatment.

TABLE 3.1.1.1
EFFECT OF TELMISARTAN ON SURVIVAL IN RATS, 26 WEEKS ORAL ADMINISTRATION

Dose	# of deaths		Study		Macroscopic and microscopic findings
(mg/kg/day)	M	F	Wk	Day	
Control	1		25	174	Died during anesthesia for blood collection. Hemorrhage and emphysema in lungs.
50 mg telmisartan		1	10	66	Sacrificed moribund. Stomach: severe dilatation, contents bloody, suspected mucosal erosions; cecum: dilatation, discoloration, dark red contents, edema and hemorrhage; liver: necrosis, gray-white discoloration; lung: some red focal discolorations; mesenteric lymph node with red focal discolorations.
15.6 mg HCTZ		1	8	54	Died of acute intra-abdominal bleeding. Amber colored liquid in the thorax; heart: moderate congestion; lung: edema; rectum- severe hemorrhage; urinary bladder: severe dilatation, severe hemorrhage in adjacent tissue.
15.6 mg HCTZ (toxicokinetic group)		1	16	106	Dead. Not examined

No clinical signs considered of toxicological importance or drug-related were recorded during the study.

Body weight gain was dose-dependently reduced for males at all dose levels at weeks 13 and 26 of treatment. Body weight at the low dose was not significantly different from that of the vehicle control. However, at 4/1.25 mg/kg/day telmisartan/HCTZ, body weight was mildly reduced (7 and 11% in study weeks 13 and 26, respectively) compared to the vehicle control. Animals receiving 50 mg/kg/day telmisartan, with or without HCTZ, showed a similar percent reduction in body weight relative to control (14 to 15 % at 13 weeks and 16 to 18% at 26 weeks), suggesting the absence of a modulating effect of HCTZ on the effect of telmisartan on body weight development. Animals in the high dose recovery group still showed a moderate reduction (8%, not significantly different from age matched control) in body weight at the 8th week following cessation of treatment (Table 3.1.1.2, Fig 3.1.1.1).

TABLE 3.1.1.2
EFFECT OF TELMISARTAN WITH OR WITHOUT HCTZ ON BODY WEIGHT AND BODY WEIGHT GAIN OF MALE RATS IN 26 WEEK TOXICITY STUDY

Study wk	Body weight change parameters	Dose: Telmisartan/HCTZ mg/kg/day						
		Control	0.1/0.03	4/1.25	50/7.8	50/15.6	50/0	0/15.6
-1	Mean absolute b. wt., g	317.9	321.6	321.5	316.6	320.1	316.5	322.1
	Deviation of b. wt. relative to control (%)	-	1	1	0	1	0	1
13	Mean absolute b. wt., g	465.3	462.8	435.2↓	393.8↓	401.1↓	402.3↓	453.3
	Deviation of b. wt. relative to control (%)	-	-1	-7	-15	-14	-14	-3
	B. wt. gain (%)¶	46.4	44.0	35.4	24.4	25.3	27.1	40.7
26	Mean absolute b. wt., g	516.2	507.7	460.4↓	421.7↓	427.5↓	435.2↓	493.0↓
	Deviation of body wt. relative to control (%)	-	-2	-11	-18	-17	-16	-5
	B. wt. gain (%)¶	62.4	57.9	43.2	33.2	33.6	37.5	53.1
34	Mean absolute b. wt., g	525.9	-	-	-	486.6	-	-
	Deviation of body wt. relative to control (%)	-				-8		
	B. wt. gain (%)¶	65.4				52.0		

¶ : percent increase relative to start of administration; calculations done using means presented above.
↓ : decrease statistically significant relative to the vehicle control ($p < 0.05$, t-test, pooled variance)

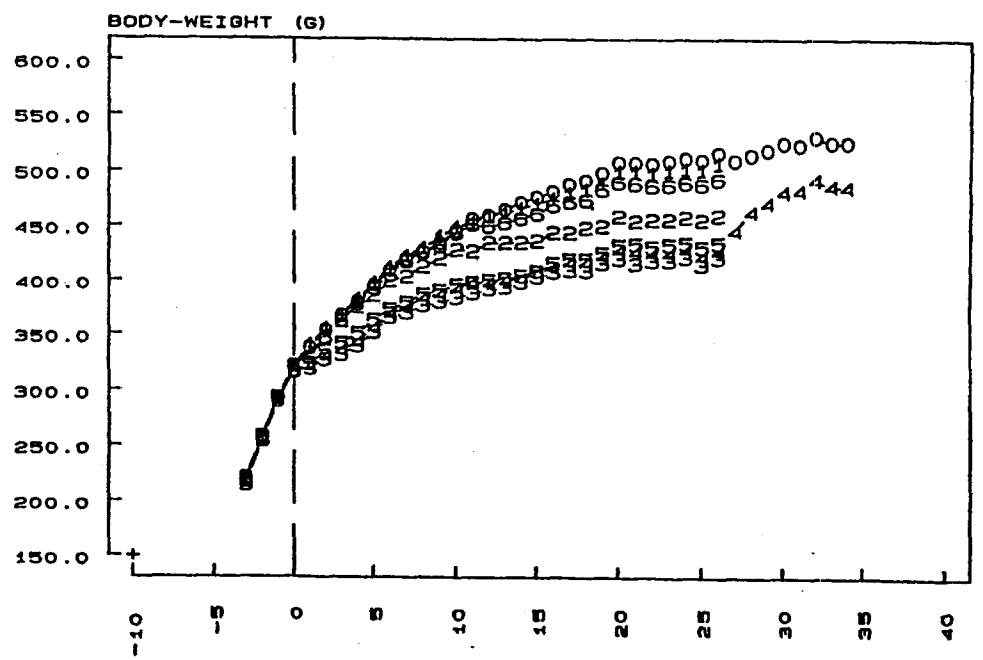

Fig. 3.1.1.1.: 26-week toxicity of telmisartan/HCTZ. Group mean body weight changes in male rats. X axis: week. Numerals indicate dose groups, viz., 0: Control; 1: 0.1/0.03; 2: 4.0/1.25; 3: 50/7.8; 4: 50.0/15.6; 5: 50.0/0; 6: 0/15.6 mg/kg/day telmisartan/HCTZ.

For females, a dose-dependent decrease in body weight (2 to 6%) relative to the vehicle control was noted in study week 13 only. A modulating effect of HCTZ on telmisartan is not conspicuous (Table 3.1.1.3, Fig. 3.1.1.2).

TABLE 3.1.1.3
EFFECT OF TELMISARTAN WITH OR WITHOUT HCTZ ON BODY WEIGHT AND BODY WEIGHT GAIN OF FEMALE RATS IN 26 WEEK TOXICITY STUDY

Study wk	Body weight change parameters	Dose: Telmisartan/HCTZ mg/kg/day						
		Control	0.1/0.03	4/1.25	50/7.8	50/15.6	50/0	0/15.6
-1	Mean absolute b. wt., g	216.8	216.1	215.4	212.5	211.9	212.1	216.0
	Deviation of b. wt. relative to control (%)	-	0	-1	-2	-2	-2	0
13	Mean absolute b. wt., g	265.4	263.5	260.6	258.1	250.2↓	260.4	264.9
	Deviation of b. wt. relative to control (%)	-	-1	-2	-3	-6	-2	0
	B. wt. gain (%)¶	22.4	21.9	21.0	21.5	18.1	22.8	22.6
26	Mean absolute b. wt., g	278.0	277.2	264.9↓	270.4	266.6↓	274.9	273.7
	Deviation of body wt. relative to control (%)	-	0	-5	-3	-4	-1	-2
	B. wt. gain (%)¶	28.2	28.3	23.0	27.2	25.8	29.6	26.7
34	Mean absolute b. wt., g	288.6	-	-	-	277.8	-	-
	Deviation of body wt. relative to control (%)	-				-4		
	B. wt. gain (%)¶	33.1				31.1		

¶ : percent increase relative to start of administration; calculations done using means presented above.
↓ : decrease statistically significant relative to the vehicle control ($p < 0.05$, t-test, pooled variance)

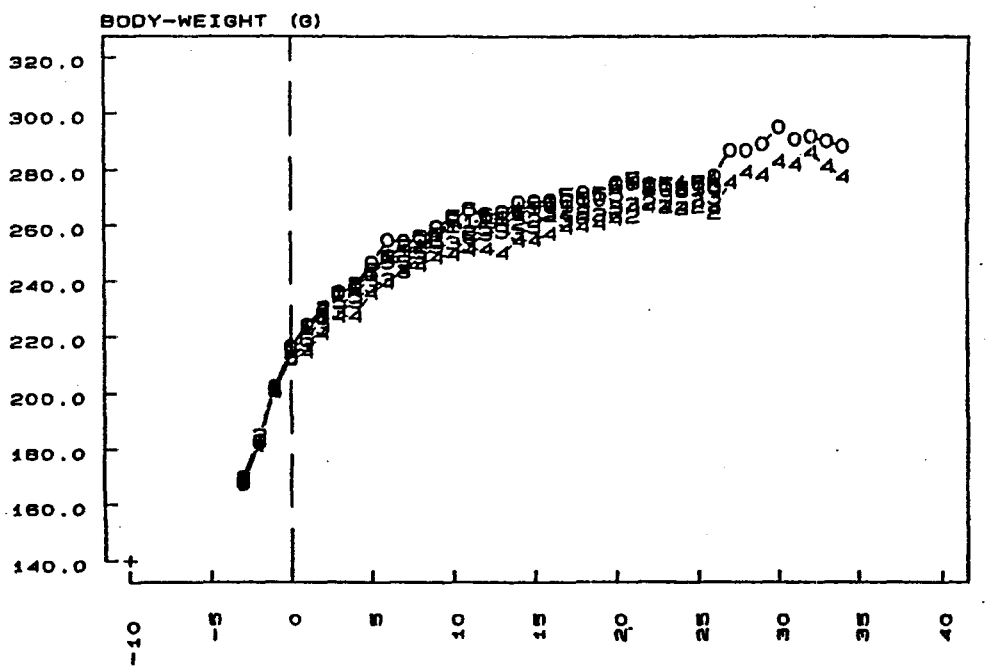

Fig. 3.1.1.2.: 26-week toxicity of telmisartan/HCTZ. Group mean body weight changes in female rats. X axis: week. See Fig. 3.1.1.1. for details.

A dose-dependent decrease in food consumption for males was noted in all weeks of measurement. The values were significantly different from vehicle control for 50 mg/kg telmisartan groups with or without HCTZ. The values were similar to control at the end of the recovery period (Table 3.1.1.4). For females, no significant differences in food consumption were noted except for a lower than control consumption for the group receiving 50/15.6 mg/kg/day telmisartan/HCTZ in study week 13 (Table 3.1.4).

TABLE 3.1.1.4
EFFECT OF TELMISARTAN WITH OR WITHOUT HCTZ ON WEEKLY FOOD CONSUMPTION IN 26 WEEK TOXICITY STUDY IN RATS

Study wk	Food consumption parameters	Dose: Telmisartan/HCTZ mg/kg/day						
		Control	0.1/0.03	4/1.25	50/7.8	50/15.6	50/0	0/15.6
Males								
-1	Mean food consumption, g	171.3	169.5	166.5	164.1↓	172.9	162.9↓	171.5
	% Deviation rel to control	-	-1	-3	-4	1	-5	0
13	Mean food consumption, g	169.1	164.8	160.5	152.7↓	148.6↓	151.9↓	167.6
	% Deviation rel to control	-	-3	-5	-10	-12	-10	-1
26	Mean food consumption, g	167.0	165.0	155.9↓	150.5↓	150.6↓	151.2↓	164.6
	% Deviation rel to control	-	-1	-7	-10	-17	-10	-1
34	Mean food consumption, g	160.0	-	-	-	160.9	-	-
	% Deviation rel to control	-				1		
Females								
-1	Mean food consumption, g	122.5	120.2	119.8	116.4↓	118.5	116.4↓	122.4
	% Deviation rel to control	-	-2	-2	-5	-3	-5	0
13	Mean food consumption, g	120.1	117.7	121.3	116.8	113.3↓	113.9	119.2
	% Deviation rel to control	-	-2	1	-3	-6	-5	-1
26	Mean food consumption, g	116.7	117.4	116.0	115.0	113.3	111.1	117.6
	% Deviation rel to control	-	1	-1	-2	-3	-5	1
34	Mean food consumption, g	113.2	-	-	-	118.0	-	-
	% Deviation rel to control	-				4		

↓ : decrease statistically significant relative to the vehicle control ($p < 0.05$, t-test, pooled variance)

Water consumption for males receiving 0.1/0.03 and 4/1.25 mg/kg/day telmisartan/HCTZ was comparable to control. Markedly increased water consumption was observed in animals receiving 50 mg telmisartan/kg/day with HCTZ. Slightly elevated water intake was noted in animals given 50 mg telmisartan/kg/day alone. In contrast, a trend to decreased water consumption was noted in animals receiving 15.6 mg HCTZ/kg/day alone. A similar observation was made with females except that the consumption was moderate and restricted to high dose

groups receiving telmisartan alone. As in males, a trend to decreased water consumption was noted in females receiving 15.6 mg HCTZ/kg/day alone. Water consumption decreased slightly in recovery animals of both sexes (Table 3.1.1.5).

TABLE 3.1.1.5
EFFECT OF TELMISARTAN WITH OR WITHOUT HCTZ ON WEEKLY WATER CONSUMPTION IN 26 WEEK TOXICITY STUDY IN RATS

Study wk	Water consumption parameters	Dose: Telmisartan/HCTZ mg/kg/day						
		Control	0.1/0.03	4/1.25	50/7.8	50/15.6	50/0	0/15.6
Males								
-1	Mean water consumption, g	252.4	246.5	243.5	241.2	252.7	240.2	246.1
	% Deviation rel to control	-	-2	-4	-4	0	-5	-3
13	Mean water consumption, g	175.9	169.5	174.6	273.9	283.1	220.2	155.0
	% Deviation rel to control	-	-4	-1	56	61	25	-12
26	Mean water consumption, g	160.4	159.6	171.9	305.5	314.6	224.2	146.7
	% Deviation rel to control	-	-1	7	91	96	40	-9
34	Mean water consumption, g	191.0	-	-	-	178.9	-	-
	% Deviation rel to control	-				-6		
Females								
-1	Mean water consumption, g	194.5	193.4	196.7	186.7	192.5	193.5	189.9
	% Deviation rel to control	-	-1	1	-4	-1	-1	-2
13	Mean water consumption, g	145.0	152.6	146.7	180.7	184.0	147.8	133.3
	% Deviation rel to control	-	5	1	25	27	2	-8
26	Mean water consumption, g	148.1	148.3	154.1	175.0	183.0	149.4	134.6
	% Deviation rel to control	-	0	4	18	24	1	-9
34	Mean water consumption, g	175.9	-	-	-	164.7	-	-
	% Deviation rel to control	-				-6		

No changes from concurrent control were noted for blood pressure in groups treated with 0.1/0.3 mg/kg/day telmisartan/HCTZ or HCTZ alone. In the other groups, a dose-dependent decrease in blood pressure was observed with the greatest effect seen when 50 mg/kg/day telmisartan was administered in combination with 7.8 or 15.6 mg/kg/day HCTZ. Hypotension was most prominent in week 5 when doses of 4/1.25, 50/7.8, 50/15.6 and 50/0 mg/kg/day telmisartan/HCTZ reduced diastolic blood pressure by 29, 64, 64 and 50%, respectively. A similar trend was seen for measurements made during weeks 13 and 25. This suggests a clear potentiating effect of HCTZ on telmisartan. Heart rate slightly but significantly increased in combination groups relative to vehicle control, possibly a reflex response to the marked decrease in blood pressure rather than a direct effect on heart rate.

Hematological findings included dose-dependent decreases in erythrocytic parameters (RBC, hemoglobin, hematocrit). The decreases were statistically significant for females receiving 4/1.25 or more mg/kg/day telmisartan/HCTZ and for males receiving 50/7.8 or more mg/kg/day telmisartan/HCTZ. HCTZ alone had no relevant influence on red cell count parameters (Table 3.1.1.6). All three parameters returned to normal levels after the recovery period. Marginal changes (± 4%, $p > 0.05$) were observed in mean corpuscular hemoglobin (MCH), mean corpuscular volume (MCV) and mean corpuscular hemoglobin concentration (MCHC) in the high dosage groups. A moderate (11%) and significant decrease in platelet count was noted at week 13 for female rats receiving 50/7.8 mg/kg/day telmisartan/HCTZ. At all study weeks, thromboplastin (prothrombin) time was decreased ($p < 0.05$) in both sexes receiving high doses (also mid dose in case of females) of telmisartan with or without HCTZ. (Table 3.1.1.6). The sponsor considers all the above findings a consequence of the pharmacological activity of telmisartan rather than toxicity. Anemia is a class effect as it is observed with other sartans in both rats and dogs. However, there is no evidence that thrombocytopenia and decreased thromboplastin time are class effects. Clinically, thrombocytopenia is one of the adverse effects reported with HCTZ.

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TABLE 3.1.1.6
EFFECT OF TELMISARTAN WITH OR WITHOUT HCTZ ON HEMATOLOGY PARAMETERS IN 26 WEEK TOXICITY STUDY IN RATS

Parameter	Wk	Sex	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	
			mean	mean	Δ%	mean	Δ%	mean	Δ%	mean	Δ%	mean	Δ%	mean	Δ%
Erythro-cytes (10^6/ul)	4	M	8.0	8.2	2	7.9	-2	7.3$^{\$}$	-9	7.3$^{\$}$	-9	7.6$^{\$}$	-5	8.2	2
		F	7.6	7.8	2	7.5	-2	6.4$^{\$}$	-16	6.5$^{\$}$	-15	6.8$^{\$}$	-11	7.7	1
	13	M	8.2	8.3	2	8.2	0	7.0$^{\$}$	-14	7.0$^{\$}$	-15	7.3$^{\$}$	-11	8.2	0
		F	7.8	7.8	0	7.4$^{\$}$	-5	6.5$^{\$}$	-17	6.5$^{\$}$	-16	6.8$^{\$}$	-13	7.9	1
	25	M	8.4	8.7	3	8.4	-1	7.1$^{\$}$	-16	7.0$^{\$}$	-18	7.4$^{\$}$	-13	8.9$^{\$}$	6
		F	8.0	8.1	1	7.6$^{\$}$	-6	7.1$^{\$}$	-11	7.0$^{\$}$	-13	7.2$^{\$}$	-10	8.2	2
	33	M	8.1							8.2	2				
		F	7.8							7.7	-1				
Hemoglo-bin (g/100ml)	4	M	16.0	16.2	1	15.7	-2	14.7$^{\$}$	-8	14.9$^{\$}$	-7	15.1$^{\$}$	-6	16.2	1
		F	15.46	15.4	0	14.9*	-3	12.9$^{\$}$	-16	13.1$^{\$}$	-15	13.7$^{\$}$	-11	15.3	0
	13	M	16.2	16.2	0	15.9	-2	14.3$^{\$}$	-11	14.2$^{\$}$	-12	14.6$^{\$}$	-10	16.0	-1
		F	16.1	16.0	0	15.3$^{\$}$	-5	13.8$^{\$}$	-14	13.8$^{\$}$	-14	14.0$^{\$}$	-13	16.2	0
	25	M	17.2	17.4	1	17.0	-1	15.0$^{\$}$	-13	14.6$^{\$}$	-15	15.3$^{\$}$	-11	17.4	1
		F	16.5	16.7	1	15.7$^{\$}$	-5	14.9$^{\$}$	-10	14.7$^{\$}$	-11	14.8$^{\$}$	-10	16.8	2
	33	M	16.8							17.1	2				
		F	16.5							16.3	-1				
Hemato-crit (vol%)	4	M	44.6	45.3	2	43.5*	-2	40.1$^{\$}$	-10	40.6$^{\$}$	-9	42.0$^{\$}$	-6	45.9*	3
		F	42.7	43.3	1	41.5*	-3	35.8$^{\$}$	-16	36.0$^{\$}$	-16	37.7$^{\$}$	-12	43.2	1
	13	M	45.5	46.2	1	45.7	0	40.0$^{\$}$	-12	39.5$^{\$}$	-13	41.3$^{\$}$	-9	46.0	1
		F	44.1	44.4	0	42.0$^{\$}$	-5	37.0$^{\$}$	-16	37.1$^{\$}$	-16	38.4$^{\$}$	-13	44.7	1
	25	M	47.2	48.6	3	47.2	0	40.7$^{\$}$	-14	40.0$^{\$}$	-15	42.0$^{\$}$	-11	50.0$^{\$}$	6
		F	46.1	46.6	1	43.4$^{\$}$	-6	41.2$^{\$}$	-11	40.3$^{\$}$	-13	41.4$^{\$}$	-10	46.9	2
	33	M	45.6							46.4	2				
		F	44.4							44.3	0				
Prothrom-bin time (sec)	4	M	20.6	20.6	0	20.4	-1	19.5$^{\$}$	-5	19.2$^{\$}$	-7	19.6$^{\$}$	-5	20.8	1
		F	18.1	18.3	1	18.5	2	17.8	-2	17.6*	-3	18.5	2	18.5	2
	13	M	19.6	20.1	2	19.6	0	18.4$^{\$}$	-6	18.5$^{\$}$	-6	19.2	-2	19.7	0
		F	18.5	18.2	-2	18.0*	-3	17.2$^{\$}$	-7	17.4$^{\$}$	-6	17.8$^{\$}$	-4	18.7	1
	25	M	20.6	20.7	0	20.3	-2	19.3$^{\$}$	-6	18.9$^{\$}$	-8	19.4$^{\$}$	-6	20.8	1
		F	19.1	18.9	-1	18.4*	-3	17.4$^{\$}$	-9	17.8$^{\$}$	-7	18.3$^{\$}$	-4	18.6	-3
	33	M	19.8							19.1	-3				
		F	17.9							18.0	0				

*: $p < 0.05$; $^{\$}$: <0.01 Significant when compared with control
Δ% : deviation from concurrent vehicle control

Biochemical findings included slight but dose-dependent increases ($p < 0.05$) in alkaline phosphatase in females receiving 4/1.25 or more mg/kg/day telmisartan/HCTZ. Higher than control levels of total bilirubin ($p < 0.05$) were observed in rats dosed with the combination of the highest dose of telmisartan and the highest dose of HCTZ in certain weeks of measurement (25^{th} week in males and 4^{th} week in females). Total cholesterol was increased ($p < 0.01$) in both male and female rats dosed at 50 mg telmisartan/kg/day in combination with either dose of HCTZ. The increase was small with telmisartan alone, and HCTZ alone had no effect. The values returned to normal levels in the recovery group. Total glycerol was decreased independent of HCTZ in male rats receiving 4 or more mg telmisartan/kg/day. At the end of the recovery period total glycerol was still below control ($p > 0.05$) in both sexes. Dose-dependent increases ($p < 0.05$-0.01 at 4/1.25 or more mg/kg/day telmisartan/HCTZ) in blood urea nitrogen were noted in male and female animals. A mean increase of over 300% was observed in male rats dosed at 50 mg telmisartan/kg/day in combination with either dose of HCTZ. HCTZ alone showed only slight, mostly insignificant increases, higher in males than in females. The increase was largely reversible at the end of the recovery period, though the values were still statistically significant in males relative to control. Increases in creatinine values over control were observed at the high dose of telmisartan with or without HCTZ (increases higher in males than in females). The increase was reversible at the end of the recovery period. A dose-dependent decrease in total protein was observed for both mono and combination groups. At the low dose, the difference from vehicle control was statistically significant for females only (Table 3.1.1.7).

Mild increases ($p < 0.05$-0.01) in potassium and magnesium were observed in plasma of rats receiving 4 or more mg telmisartan/kg/day with or with out HCTZ. The values returned to normal after the recovery period. HCTZ alone, in contrast, decreased ($p < 0.05$-0.01) levels of both potassium and magnesium, as well as levels of inorganic phosphate (Table 3.1.1.7).

TABLE 3.1.1.7
EFFECT OF TELMISARTAN WITH OR WITHOUT HCTZ ON BLOOD CHEMISTRY DURING 26 WEEK TOXICITY STUDY IN RATS
(Results expressed as group mean values)

Parameter	Wk	Sex	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	
			mean	mean	Δ%	mean	Δ%	mean	Δ%	mean	Δ%	mean	Δ%	mean	Δ%
Alkaline Phospha-tase (U/l)	4	M	262	265	1	279	6	270	3	256	-2	255	-3	271	3
		F	174	188	8	205*	18	210§	21	202*	16	214§	23	171	-2
	13	M	175	180	3	185	6	202§	15	186	6	183	5	170	-3
		F	147	159	8	169	15	159	9	177*	20	164	11	143	-2
	25	M	188	197	5	205	9	195	4	189	1	193	3	185	-1
		F	133	151	13	179§	34	146	9	162*	22	147	10	139	4
	33	M	176							171	-3				
		F	114							118	4				
Total choles-terol (mmol/l)	4	M	1.6	1.6	0	1.6	1	2.1§	28	2.2§	33	2.0§	24	1.6	-4
		F	2.0	2.0	-2	2.1	3	2.2	9	2.2*	10	2.0	0	2.0	-4
	13	M	1.6	1.6	0	1.7	5	2.1§	34	2.2§	39	2.0§	27	1.5	-7
		F	1.9	1.8	-4	2.0	4	2.2§	16	2.2§	13	2.0	7	1.7	-10
	25	M	1.6	1.7	1	1.6	-1	2.2§	35	2.2§	36	2.0§	22	1.5	-8
		F	2.1	2.0	-4	2.2	4	2.3	12	2.3*	14	2.1	3	1.9	-6
	33	M	1.8							1.6*	-12				
		F	2.3							2.1	-10				
Total glycerol (mmol/l)	4	M	1.6	1.8	11	1.5	-6	1.3	-21	1.5	-9	1.5	-8	2.0	20
		F	2.0	1.8	-11	1.6	-19	2.0	-3	2.0	-3	1.8	-13	1.5	-26
	13	M	2.3	2.3	-3	2.0	-15	1.4§	-41	1.5§	-36	1.4§	-41	2.1	-12
		F	2.6	2.7	3	2.3	-11	2.6	-2	2.7	2	2.4	-8	2.4	-10
	25	M	2.2	2.2	1	1.5§	-33	1.1§	-48	1.2§	-44	1.2§	-46	1.9	-14
		F	2.6	2.8	5	2.6	-2	2.6	0	2.8	5	2.7	1	2.3	-12
	33	M	2.4							1.8	-26				
		F	2.8							1.8	-36				
BUN (mmol/l)	4	M	8.5	9.0	6	13.1§	53	25.1§	195	24.6§	189	18.4§	116	9.6	13
		F	8.1	7.8	-4	10.2*	26	22.6§	180	22.6§	180	14.7§	82	8.3	3
	13	M	8.0	8.5	6	12.8§	59	31.3§	289	32.7§	307	21.4§	166	10.4	29
		F	9.1	8.9	-2	13.9§	53	24.5§	169	27.1§	198	15.5§	70	9.9	9
	25	M	8.4	8.8	5	15.8§	88	34.7§	313	35.8§	326	24.6§	193	11.0*	30
		F	7.8	8.5	9	12.1§	55	19.9§	154	23.0§	193	14.6§	86	8.9	14
	33	M	8.2							9.3§	13				
		F	8.7							8.4	-4				

Parameter	Wk	Sex	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	
			mean	mean	Δ%	mean	Δ%	mean	Δ%	mean	Δ%	mean	Δ%	mean	Δ%
Creatinine (µmol/l)	4	M	44.2	44.7	1	44.7	1	50.0§	13	51.1§	16	46.3	5	42.0	-5
		F	44.9	42.5	-5	43.7	-3	52.1§	16	51.8§	15	48.6§	8	44.0	-2
	13	M	47.3	47.2	0	47.1	0	54.5§	15	58.4§	24	52.9§	12	47.7	1
		F	49.5	47.7	-4	48.6	-2	52.9	7	54.8§	11	51.3	4	50.1	1
	25	M	43.7	43.3	-1	45.4	4	54.5§	25	55.7§	28	50.5§	16	45.2	3
		F	45.5	45.8	1	46.4	2	48.6	7	50.2§	10	49.1*	8	44.9	-1
	33	M	48.9							48.0	-2				
		F	49.0							50.6	3				
Total protein (g/l)	4	M	58.1	59.2	2	56.9	-2	55.4§	-5	57.0	-2	57.5	-1	59.3	2
		F	61.8	60.3	-2	58.2§	-6	55.7§	-10	56.9§	-8	56.6§	-8	59.6*	-4
	13	M	60.3	61.0	1	59.2	-2	56.8§	-6	57.4§	-5	57.1§	-5	59.6	-1
		F	65.7	63.8*	-3	60.0§	-9	59.6§	-9	59.5§	-9	60.6§	-8	62.4§	-5
	25	M	61.9	61.6	-1	58.3§	-6	57.1§	-8	57.3§	-7	57.7§	-7	60.4*	-2
		F	64.8	62.8*	-3	60.2§	-7	60.9§	-6	60.6§	-6	60.5§	-7	62.1*	-4
	33	M	64.7							60.7§	-6				
		F	69.4							65.2*	-6				
Potassium (mmol/l)	4	M	4.9	5.0	1	5.3§	8	5.6§	15	5.7§	16	5.8§	18	4.6*	-6
		F	4.5	4.3	-3	4.9§	9	5.3§	20	5.2§	17	5.3§	19	4.1§	-7
	13	M	4.9	4.9	1	5.0	3	6.0§	22	6.0§	23	5.9§	22	4.5§	-8
		F	4.5	4.6	2	5.1§	14	5.2§	15	5.2§	16	5.4§	19	4.4	-3
	25	M	4.7	4.8	2	5.1*	8	6.0§	27	6.2§	30	6.4§	34	4.5*	-5
		F	4.8	4.6	-4	5.2§	8	5.1§	7	5.2§	9	5.4§	13	4.3§	-11
	33	M	4.5							4.5	0				
		F	4.3							4.4	3				
Magnesium (µmol/l)	4	M	0.7	0.7	-3	0.7*	-9	0.9§	19	0.9§	26	0.8	2	0.6§	-16
		F	0.8	0.8*	-6	0.8*	-8	1.0§	26	1.0§	21	0.9	4	0.7§	-17
	13	M	0.7	0.7	-4	0.7	-8	1.0§	30	1.1§	50	0.9§	18	0.6§	-17
		F	0.8	0.8	-2	0.7*	-9	1.1§	31	1.1§	40	0.9*	7	0.7§	-17
	25	M	0.7	0.7	-2	0.7	-2	1.1§	47	1.2§	60	1.0§	32	0.6§	-18
		F	0.8	0.8	2	0.8	-2	1.0§	27	1.1§	35	0.9§	11	0.7§	-19
	33	M	0.8							0.9§	9				
		F	0.8							0.8	0				
Inorganic phosphate (mmol/l)	4	M	2.0	1.9	-4	1.8*	-7	1.9	-3	1.9	-4	1.8*	-8	1.7§	-14
		F	1.8	1.6*	-10	1.6*	-10	1.8	0	1.8	1	1.7*	-8	1.5§	-19
	13	M	1.7	1.6	-5	1.6	-4	1.7	2	1.7	4	1.6	-1	1.4§	-14
		F	1.4	1.4	0	1.4	-3	1.7§	19	1.7§	18	1.6	8	1.4	-5
	25	M	1.4	1.4	0	1.4	-4	1.6§	10	1.6§	15	1.6§	10	1.2§	-13
		F	1.2	1.3	6	1.3	1	1.5§	24	1.5§	24	1.5§	20	1.2	-2
	33	M	1.5							1.5	1				
		F	1.3							1.3	1				

*: $p < 0.05$; §: <0.01 Significant when compared with control

Δ% : deviation from concurrent vehicle control calculated before rounding the original data

There was a slight increase in urine volume in male animals and a more pronounced increase in females receiving 4.0/1.25 mg/kg/day telmisartan/HCTZ in week 14 and 24. In contrast, animals receiving high dose telmisartan, with or without HCTZ, showed a decrease in urine volume (Table 3.1.1.8). A rebound effect of increased volume was noted in high dose groups after the recovery period. HCTZ alone increased urine volume. Urine density was slightly but significantly elevated in males and females in the high dose telmisartan groups, with or without HCTZ, at all times of investigation. The values were normalized after the recovery period. The sponsor did not determine the effect of treatment on the urinary excretion of sodium and chloride. HCTZ by itself is known to increase excretion of sodium and chloride.

TABLE 3.1.1.8
EFFECT OF TELMISARTAN WITH OR WITHOUT HCTZ ON URINALYSES DURING 26 WEEK TOXICITY STUDY IN RATS.
Results expressed as group mean values

Parameter	Week	Sex	Telmisartan/HCTZ (mg/kg/day)											
			0	0.1/0.03		4.0/1.25		50/7.8		50/15.6		50/0		0/15.6	
			mean	mean	Δ%	mean	Δ%	mean	Δ%	mean	Δ%	mean	Δ%	mean	Δ%
Urine volume (ml/5 h)	14	m	11.7	11.4	-3	13.4*	15	4.9*	-58	6.0*	-49	6.4*	-45	13.4*	14
		f	5.4	5.6	4	7.1*	31	5.0	-7	4.1*	-24	4.9	-9	7.6*	41
	24	m	11.7	10.9	-7	11.3	-4	5.9*	-50	6.9*	-42	6.6*	-44	12.2	4
		f	5.5	5.4	-2	7.4*	35	4.8	-13	4.4*	-20	5.2	-6	7.6*	39
	33	m	8.5							11.3*	34				
		f	4.3							5.9*	37				
Urine density (g/ml)	14	m	1.006	1.007*	0	1.009*	0	1.017*	1	1.016*	1	1.017*	1	1.008*	0
		f	1.012	1.011	0	1.011	0	1.017*	1	1.017*	1	1.017*	0	1.008*	0
	24	m	1.011	1.011	0	1.015*	0	1.019*	1	1.018*	1	1.021*	1	1.012	0
		f	1.016	1.014*	0	1.016	0	1.021*	0	1.021*	0	1.018	0	1.012*	0
	33	m	1.016							1.012*	0				
		f	1.022							1.015*	-1				

*: $p < 0.05$ Significantly different when compared with control
Δ% : deviation from concurrent vehicle control calculated before rounding the original data

The most notable organ weight finding was a decrease in heart weight, statistically significant relative to concurrent control, irrespective of whether the comparison was done on an absolute or relative basis (whether relative to body or to brain weight). The finding was limited to telmisartan and telmisartan/HCTZ treated groups. In males, the decrease was statistically significant only for groups receiving the high dose of telmisartan (Table 3.1.1.9). In females, the decrease was statistically significant for groups receiving 4 or more mg/kg telmisartan (Table 3.1.1.10). The largest difference from control weight occurred in the male group receiving 50/7.8 mg/kg/day (24% absolute, 22% relative to brain weight) and the female group receiving 50/7.8 mg/kg/day (14% absolute, 14% relative to brain weight).

Kidney weights of female rats were statistically significantly higher than concurrent control on an absolute and relative basis (relative to body or to brain weight) in groups receiving combinations of 4/1.25 or more mg telmisartan/HCTZ/kg or groups receiving telmisartan or HCTZ alone. The largest increase occurred in the group receiving 50/15.6 mg/kg/day (15%