CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20850

PHARMACOLOGY REVIEW(S)

AUG 18 1998

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA

G. Jagadeesh, Ph.D.
8-14-1998

ORIGINAL SUBMISSION DATE September 26, 1997
CENTER RECEIPT DATE September 26, 1997
REVIEWER RECEIPT DATE September 29, 1997

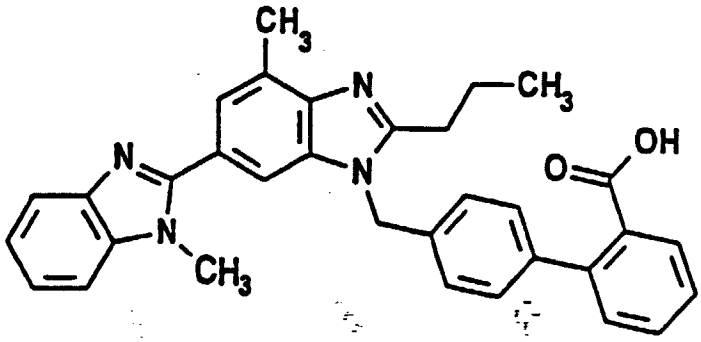
SPONSOR Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Road
PO Box 368
Ridgefield, CT 06877

DRUG PRODUCT Micardis® (Telmisartan) Tablets

DRUG CHEMISTRY

USAN Name: 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

Structural Formula



M.W. 514.63

PHARMACOLOGICAL CLASS Angiotensin II receptor antagonist

INDICATION Hypertension

FORMULATION Each tablet for oral administration contains 40 or 80 mg of telmisartan. Inactive ingredients in the tablet are povidone, sodium hydroxide, meglumine, sorbitol and magnesium stearate.

PROPOSED DOSAGE REGIMEN 80 mg once daily. Although doses up to 160 mg once daily have been studied in hypertensive patients, proposed labeling notes that a "greater effect on blood pressure may be expected from the addition of a diuretic, than from increasing the dose of Micardis® above 80 mg", should additional blood pressure reduction be required.

IND UNDER WHICH CLINICAL TRIALS WERE CONDUCTED

TABLE OF CONTENTS

INTRODUCTION

The renin-angiotensin-aldosterone system (RAAS) is of major importance for the regulation of cardiovascular function and body fluid composition. Its active molecule, angiotensin II, elicits some important pharmacological effects such as, an increase in blood pressure and vascular contraction, release of aldosterone from the adrenals and modulation of central effects such as drinking behavior. Orally active angiotensin converting-enzyme inhibitors such as captopril effectively prevent these functions of the RAAS. However, these compounds produce class-specific side effects such as cough, a quite frequent problem, and angioneurotic edema, a more serious but rare disorder. Another approach to blocking the functions of the RAAS is to prevent the binding of angiotensin II to its receptor. The prototype and most extensively studied compound of the angiotensin II antagonists is losartan. Since then a number of nonpeptide angiotensin II receptor antagonists have been described.

Angiotensin II exerts its effects by binding to receptors in target tissues/organs. Molecular biology and the development of angiotensin II receptor blockers have demonstrated the existence of a family of angiotensin II-receptor subtypes. The primary form of angiotensin II-receptor subtype, the AT_1 receptors, which is further subdivided into AT_{1a} and AT_{1b}, mediates vascular contractions and renal sodium reabsorption induced by angiotensin II. Thus, antagonism of angiotensin II at the AT_1 receptor consititute a new class of potential antihypertensive agents.

Current research has focused on the development of orally active nonpeptide angiotensin II receptor antagonists as new antihypertensive agents. A search for such an agent over the past few years has led to the discovery of several orally active nonpeptidic AT_1 selective angiotensin II receptor antagonists. This review summarizes the preclinical evaluation of one such nonpeptidic AT_1 selective angiotensin II receptor antagonist, telmisartan, synthesized at Boehringer Ingelheim Pharmaceuticals/Dr. Karl Thomae GmbH, Germany. The sponsor's NDA contains extensive preclinical data supporting this classification.

1. PHARMACODYNAMICS

1.1. Studies Related to Proposed Therapeutic Indication

Telmisartan is practically insoluble in water. For *in vitro* studies, it was dissolved in polyethylene glycol 200 and further dilutions were made in physiological salt solution. For oral and intravenous administration, telmisartan was dissolved in 1 M NaOH and the solution was stabilized with 1.8% (w/v) hydroxypropyl-ß-cyclodextrin. The pH of the solution was adjusted to pH 10-11 with 1 M HCl.

1.1.1. *In Vitro*

1.1.1.1. Receptor Specific Studies

The selectivity of telmisartan for angiotensin II receptors was evaluated by receptor binding techniques using the AT_1 receptor predominant rat lung membrane. Telmisartan displaced specifically bound ^{125}I-angiotensin II from binding sites in rat lung (Fig 1.1.1A), with high affinity (K_i 3.7 ± 1.7 nM). Telmisartan had six times the affinity of losartan (K_i 24 ± 4 nM) in this preparation. In contrast, up to 10 µM telmisartan had no interaction with angiotensin II receptors in adrenal medulla (Fig. 1.1.1B) which are of the AT_2 subtype. The effect of telmisartan on the binding of ^{125}I-angiotensin II to AT_1 receptors was further investigated in saturation experiments in rat lung preparations. As shown by Scatchard analysis of the binding data, 3 nM and 10 nM telmisartan increased the K_D (dissociation constant) of the radioligand from 0.51 ± 0.03 nM to 0.82 ± 0.12 nM and 1.9 ± 0.98 nM, respectively, whereas the corresponding Bmax (maximum number of binding sites) remained unchanged (Fig. 1.1.2). These data indicate that telmisartan competitively interacts with the AT_1 receptors in this tissue.

Telmisartan was also evaluated for binding activity at various neurotransmitter receptor sites. Telmisartan had no appreciable affinity (>10 µM) for binding to receptor sites for: α- or ß-adrenergic ligands, M_1-, M_2 or M_3-muscarinic ligands, histamine, serotonin, endothelin ETA, adenosine, dopamine, neuropeptide Y, neurokinins, or imipramine. These results suggest that telmisartan had very specific affinity for angiotensin II receptors.

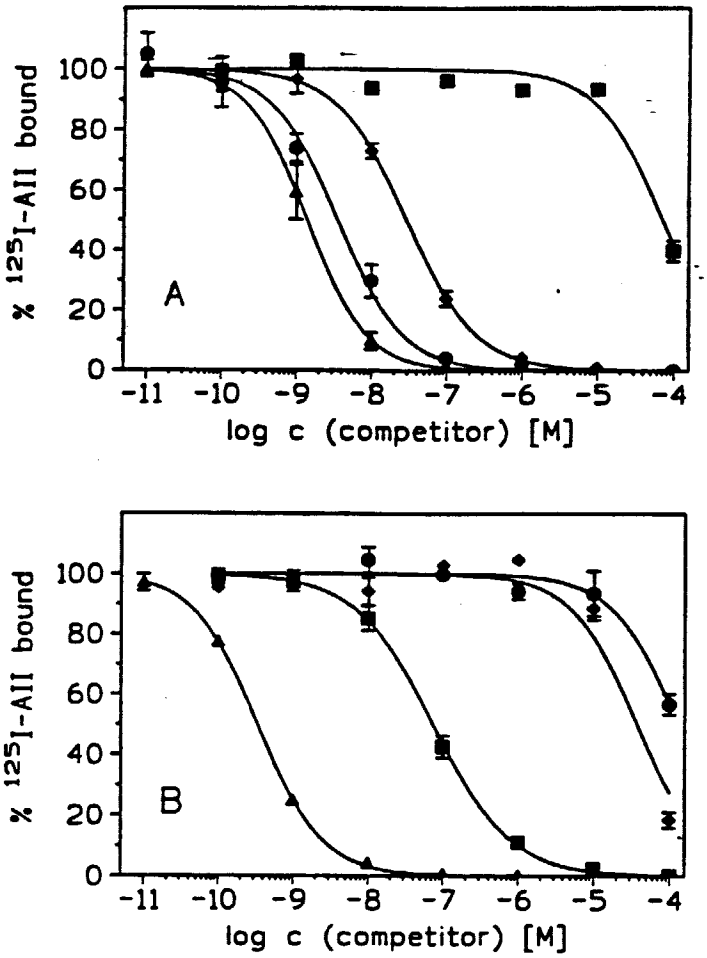


Fig 1.1.1.: Inhibition of ^{125}I-angiotensin II binding to rat lung (A: upper) and rat adrenal medulla membrane preparations (B: lower) by angiotensin II (triangles), telmisartan (circles), losartan (diamonds) and PD 123.177 (squares). Data represent the mean of three experiments run in triplicate.

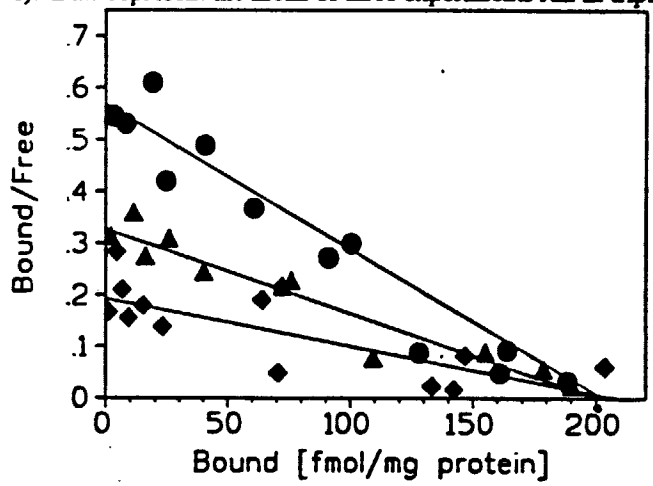


Fig. 1.1.2.: Scatchard analysis of [^{125}I]-angiotensin II binding in rat lung as determined from saturation experiments in the presence of vehicle (circles) or telmisartan [3 nM (triangles) and 10 nM (diamonds)]. Each point represents the mean of triplicate determinations. The lines were determined by regression analysis.

1.1.1.2. Studies in Isolated Tissues

Angiotensin II-induced contractions of isolated rabbit aortic rings were inhibited by telmisartan in a concentration-dependent manner. The rightward shift occurred in a parallel fashion with a decrease in maximal contractile response and the slope of the curve at all concentrations studied (Fig. 1.1.3). This is characterized as a non-competitive unsurmountable antagonism (K_B, dissociation constant 3.3 X 10^{-10}M). However, radioligand saturation binding studies showed no reduction in angiotensin II binding sites, providing evidence that telmisartan competitively interacts with AT_1 receptors. The inhibitory effects of telmisartan on the A II-induced contraction appeared specific as these concentrations had no antagonistic activity against norepinephrine- or potassium-induced contractions. Additionally, telmisartan showed no agonistic activity at any of the above concentrations.

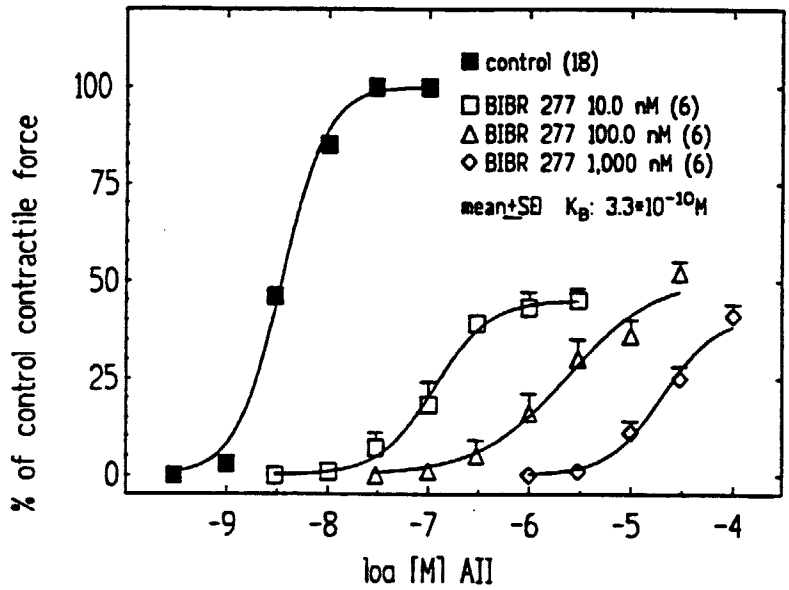


Fig. 1.1.3.: Effect of telmisartan on angiotensin II-induced contractile response in isolated rabbit aorta rings. Only one concentration of telmisartan was tested in each preparation. Values are given as percentage of the control maximum contractile force with the number of experiments in parenthesis

Further support for a competitive and reversible antagonism was provided by receptor protection studies performed in the presence of both telmisartan and the competitive antagonist losartan. In rabbit aortic rings incubated with telmisartan (0.1 μM), the angiotensin II dose response curve was markedly suppressed and displaced to the right. In preparations which were co-incubated with losartan (0.1 or 1 μM), the subsequent maximal responses of the angiotensin II concentration-response curves were displaced upwards in a concentration-related manner. If telmisartan had bound covalently (i.e. irreversibly) to the angiotensin II receptor, then co-incubation with the competitive antagonist would not have been expected to have any effect on the maximum response to angiotensin II. Thus the results show that telmisartan is a potent, specific, selective antagonist at AT_1 receptors and indicate that it is long lasting.

In further experiments, the reversibility of the antagonist-receptor interaction for telmisartan was investigated. One hour after the preincubation and thorough washing of the rat lung membranes, telmisartan still occupied 65.7 ± 3.3% of the receptors as compared to the vehicle treated membranes. Two hours after the preincubation period telmisartan showed a significantly lower receptor occupancy (46.4 ± 6.2%) as compared to the value obtained after the 1 hour dissociation period. On the other hand, competitive surmountable antagonist losartan almost completely

dissociated from AT_1 sites as indicated by a receptor occupancy of 14.3 ± 8.7% after one hour. These results suggest that the antagonist, telmisartan, demonstrates a slow off-rate from AT_1 receptor binding sites.

1.1.2. *In Vivo*

1.1.2.1. Studies in Rats (male Chbb:THOM)

A. Normotensive

a) *Per se* Effects: Since angiotensin II does not normally contribute to the maintenance of arterial pressure, an AT_1 angiotensin II receptor antagonist would not be expected to affect arterial pressure in normotensive animals. However, telmisartan, when administered orally to conscious normotensive rats in a dose of 30 mg/kg, reduced diastolic blood pressure significantly (-11%) without affecting heart rate.

b) Angiotensin II Antagonism: The ability of BIBR0277SE to selectively antagonise angiotensin II-induced pressor response was evaluated in pithed rats following i.v., intraduodenal and oral administration.

Intravenous or intraduodenal adminstration of BIBR0277SE caused a dose-related inhibition of the pressor response to angiotensin II (administered cumulatively) in this preparation. Telmisartan doses of 0.1, 0.3 and 1.0 mg/kg i.v. shifted the angiotensin II dose response curve (ED_{50}: 0.233 µg/kg) to the right by factors of 6.2, 20.2 and 86.0, respectively. In addition, the maximal increases in diastolic b.p. following angiotensin II were reduced in the presence of telmisartan. Intraduodenal administration of 0.3 and 1 mg/kg telmisartan shifted the angiotensin II dose-response curve (ED_{50}: 0.241 µg/kg) by factors of 4.4 and 9.9, respectively. Oral administration of telmisartan (1 mg/kg) shifted the angiotensin II dose-response curve by a factor of 5.5. With all three routes of administration of telmisartan, the maximal pressor response to angiotensin II was significantly depressed. This indicates that telmisartan is a noncompetitive angiotensin II receptor antagonist *in vivo*.

The effects of telmisartan 1-*O*-acylglucuronide, the main metabolite of telmisartan, on the angiotensin II pressor response in anaesthetized rats were compared to those of vehicle and the active principle, telmisartan.

Male rats were anesthetized with pentobarbital sodium. Right carotid artery, both jugular veins and the left femoral artery were cannulated for blood sampling, administration of drugs or vehicle, and measurement of arterial diastolic blood pressure, respectively. After achieving a stable baseline diastolic blood pressure (MAP), angiotensin II (0.1 µg/kg, i.v. bolus) was administered twice (with an interval of 3 min between administrations) prior to administration of vehicle or test drugs. The peak increase in diastolic b.p. following the second challenge was taken as the control angiotensin II pressor response. The angiotensin II challenge was repeated 2, 5, 15 and 30 min after the administration of vehicle or test drugs (Table 1.2.1). The pharmacokinetic profile of telmisartan and telmisartan 1-*O*-acylglucuronide was determined in

blood samples collected at various intervals after i.v. dosing and is summarized in section 2.1.4 (study #U97-2189) of this review.

Baseline diastolic blood pressure was similar and not significantly different among the groups (90 ± 3, 84 ± 2, 89 ± 1 and 88 ± 4 mmHg in the groups treated with vehicle, 1.34 or 4.02 mg/kg telmisartan 1-*O*-acylglucuronide or 1 mg/kg telmisartan, respectively). A small gradual decline in diastolic blood pressure was observed over time in the vehicle-treated and telmisartan 1-*O*-acylglucuronide-treated animals, but no significant differences could be detected. In contrast, a rapid, significant and sustained decrease in diastolic blood pressure (a reduction of approximately 30 mmHg) was observed after administration of telmisartan. The angiotensin II pressor responses in the groups treated with either the lower or the higher dose of telmisartan 1-*O*-acylglucuronide were not significantly different from those of the time-matched vehicle treated group (Table 1.2.1). In contrast, the angiotensin II pressor response was significantly inhibited (to approx. 20 to 30% of the initial control response) after administration of telmisartan.

TABLE 1.2.1
ANGIOTENSIN II PRESSOR RESPONSE OF VEHICLE, TELMISARTAN 1-*O*-ACYLGLUCURONIDE OR TELMISARTAN IN ANAESTHETIZED, NORMOTENSIVE RATS

	Angiotensin II Pressor Response (% of initial predrug response**)			
	2 min post admn	5 min post admn	15 min post admn	30 min post admn
Vehicle (n = 11)	111 ± 3	111 ± 3	118 ± 4	131 ± 9
T-glucuronide, 1.34 mg/kg (n = 6)	111 ± 4	115 ± 4	122 ± 4	121 ± 4
T-glucuronide, 4.02 mg/kg (n = 6)	100 ± 6	108 ± 9	107 ± 6	118 ± 6
Telmisartan, 1 mg/kg (n = 6)	20 ± 3 *	23 ± 4 *	29 ± 3 *	28 ± 2 *

Values are Mean ± SE
* $p < 0.05$ by Dunnett's test
** [% of initial response (= 100%)]

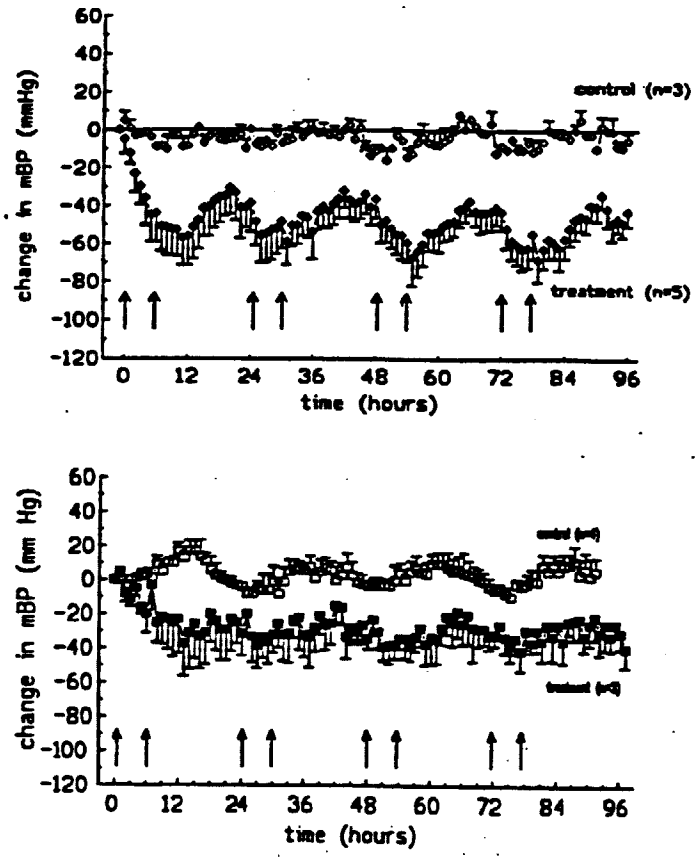
It was concluded from these results that telmisartan 1-*O*-acylglucuronide is devoid of hemodynamic effects and any angiotensin II antagonistic effect in anaesthetized rats at doses, equivalent to and three-fold higher than those of the active compound, telmisartan.

B. Hypertension Models

a) High Renin Hypertension: The dose-response effects of telmisartan, administered orally, on b.p. and heart rate were studied in the 2 kidney, 1 clip, renal hypertensive rat. Renin-dependent hypertension was established in rats by constriction of one renal artery. Blood pressure was recorded from conscious rats beginning the day after implantation of the catheters. The solutions of telmisartan (0.3 and 1 mg/kg/2 ml, bid for 4 days) were given by gavage and measurements were made at 1 hour intervals for 4 days.

At 0.3 mg/kg p.o. b.i.d, telmisartan caused a 37 ± 12 mm Hg decrease in mean arterial pressure, from a starting value of 196 ± 7 mm Hg, after 4 days of treatment. 1 mg/kg p.o. b.i.d lowered the mean arterial pressure significantly after the first dose by about 42 mm Hg, from a starting value of 200 ± 3 mm Hg. A maximum fall of 68 ± 12 mm Hg was reached after 4 days of treatment.

There were no significant changes in heart rate in either of the groups treated with 0.3 or 1 mg/kg. In the same study losartan was found to be 3 times less potent than telmisartan in lowering arterial pressure (Fig. 1.1.4).



Another study, utilizing conscious, renal hypertensive rats, evaluated the hypotensive effects of telmisartan when administered in the drinking water for 1 week at 1 mg/kg/day followed by an additional week after decreasing the dose to 0.3 mg/kg/day. The pH of the drinking drug solution was neutral. Telmisartan lowered mean arterial pressure after the first day by 36 ± 12 mm Hg from a starting value of 182 ± 7 mm Hg. After 7 days of treatment, the peak fall in blood pressure was 38 ± 2 mm Hg. When the dosage of telmisartan was reduced to 0.3 mg/kg/day, mean arterial pressure gradually increased, reaching a new level after 4 days of treatment (Fig. 1.1.5). The maximum reduction with 0.3 mg/kg/day, after 7 days, was 29 mm Hg. Heart rate was not changed with either treatment regimen.

Figure 1.1.4.: Change from baseline of mean blood pressure of renovascular hypertensive rats after oral administration of telmisartan (1 mg/kg b.i.d.; upper) or losartan (3 mg/kg b.i.d.; lower). Arrows indicate substance administration. Results are the mean ± SEM

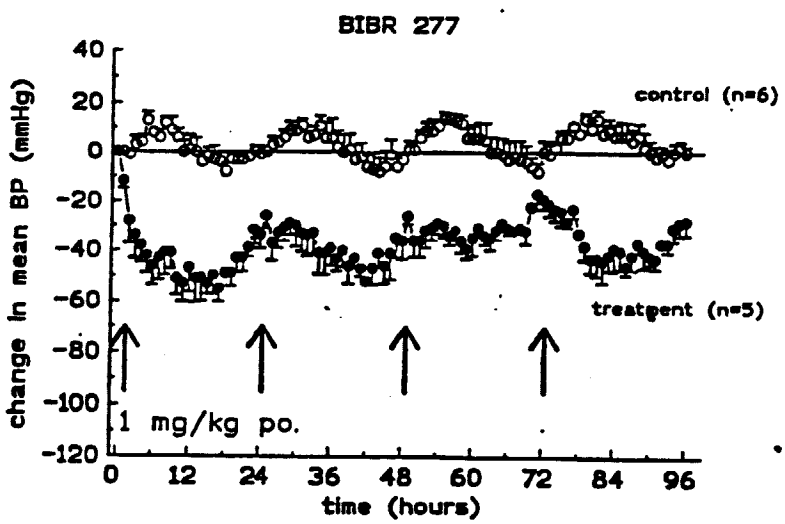


Figure 1.1.5.: Blood pressure in conscious, chronically instrumented renovascular hypertensive rats after repeated oral administration of vehicle (open symbols, n = 6) or 1.0 mg/kg/day telmisartan (closed symbols, n = 5). Data represent the mean ± standard error. The arrows indicate compound or vehicle administration.

b) Spontaneously Hypertensive Rats (SHR): Effects of telmisartan were studied on the blood pressures and heart rates of spontaneously hypertensive rats which were chronically instrumented with pressure transducers. Several weeks after the recovery from operation, an oral (gavage) dose of telmisartan at 0.3, 1.0 and 3.0 mg/kg/day was given once daily for 4 days.

Telmisartan caused a dose-dependent and sustained reduction in mean blood pressure without an effect on heart rate at all dose levels. The threshold dose for the antihypertensive effects in SHR was 0.3 mg/kg/day. The results are tabulated below.

Dose, mg/kg/day, (n)	Maximal reduction in mean blood pressure after	
	First application	4 days
0.3 (4)	14 ± 2 mm Hg	23 ± 3 mm Hg
1.0 (4)	15 ± 2	22 ± 1
3.0 (3)	27 ± 2	38 ± 4

Comparing the results with telmisartan in SHR and renal hypertensive rats (see section 1.1.2.1.B.a), it is evident that telmisartan is much more effective as an antihypertensive agent in the latter model, the one with a high renin activity.

1.1.2.2. Studies in Rabbits (male Chinchilla

The effect of i.v. and oral administration of telmisartan on the angiotensin II-mediated increase in diastolic b.p. (bolus injections of 1 μg/kg) was investigated in conscious rabbits. Intravenous administration of 0.1 mg/kg of telmisartan caused an instantaneous decrease of the angiotensin II-mediated pressor response. At 30 min and 1, 2, 3, and 5 hr after administration of telmisartan, the angiotensin II-pressor responses were still significantly inhibited. Further, the inhibitory effect was long-lasting (>5 hr). Oral administration of 0.3 and 1 mg/kg of telmisartan also showed a dose-dependent inhibition of the angiotensin II pressor response. The pressor responses were significantly inhibited at 1 hr after 1 mg/kg and 2 hr after 0.3 mg/kg of telmisartan. The responses were further significantly inhibited 4 and 6 hr after administration of telmisartan.

1.1.2.3. Studies in Dogs

a) Conscious, Normotensive Beagle Dogs: A study was conducted to investigate the effect of telmisartan, after i.v. and oral administration, on the angiotensin II-induced pressor response in conscious, normotensive, chronically instrumented male and female beagle dogs. Bolus injections of angiotensin II (0.1 μg/kg) were administered with an interval of 10 min until a consistent pressor response to angiotensin II was noted. At the dose of 0.01 mg/kg i.v., telmisartan reduced the pressor response from 54 mm Hg to 30 mm Hg at 15 min post-administration. The pressor response to angiotensin II was still significantly inhibited (40 mm Hg) at 7 hr post-dosing. With the higher intravenous dose of 0.03 mg/kg telmisartan, the pressor response to angiotensin II was 3 mm Hg and 0 mm Hg at 15 min and 60 min, respectively, post-dosing. The effect then decreased gradually, but a significant inhibition was apparent after 7 hr.

Oral administration of telmisartan (0.03, 0.1, or 0.3 mg/kg) also effectively inhibited the angiotensin II-induced pressor response in this model. The decrease in the response was dose-dependent. A more pronounced inhibitory effect, which lasted beyond 28 hr, was observed at a dose of 0.3 mg/kg. As discussed earlier in the receptor binding studies, this long duration of action could result from the slow dissociation of telmisartan from its binding sites at the vascular angiotensin II receptor.

b) Conscious, Normotensive Labrador Dogs: The above results were confirmed in a later study in conscious Labrador dogs after i.v. and oral administration. A total of 8 dogs (2 male and 2 female dogs per route) were used in the study. The interval between two doses was at least 7 days. The dogs were instrumented with a pressure transducer in the descending thoracic aorta to measure arterial blood pressure.

A bolus of 0.3 μg/kg angiotensin II (0.015 ml/kg of a saline solution) was i.v. injected before and after the administration of 3, 10, and 30 μg telmisartan/kg i.v. (0.025 to 0.03 ml/kg) and 30, 100, and 300 μg telmisartan/kg p.o. (in gelatin capsules). Angiotensin II increased diastolic b.p. in all treatment groups between 60 and 80 mm Hg. The reduction of the angiotensin II-induced increase in diastolic b.p. was used to determine the efficacy and duration of the angiotensin II receptor blocking effects of telmisartan. Telmisartan itself did not significantly change arterial diastolic blood pressure.

The hypertensive effect of angiotensin II was dose dependently and significantly blocked by telmisartan. The onset of the i.v. action was slow; maximal inhibitions of 54%, 65% and 95% were observed at 60 min after 3, at 45 min after 10, and at 15 min after 30 μg/kg i.v. The blockade lasted about 24 hours at low and mid doses and more than 24 hours at high dose. The ID_{50} (dose resulting in 50% inhibition of angiotensin II) was 2.89 μg/kg i.v.

Oral telmisartan caused maximal reductions of angiotensin II effects of 51%, 75% and 94% at 4 hr after 30, at 4 hr after 100, and at 3 hr after 300 μg/kg. The blockade lasted for about 12, 28 and 32 hr at doses of 30, 100 and 300 μg/kg p.o. The ID_{50} was calculated as 29.7 μg/kg (Fig. 1.1.6).

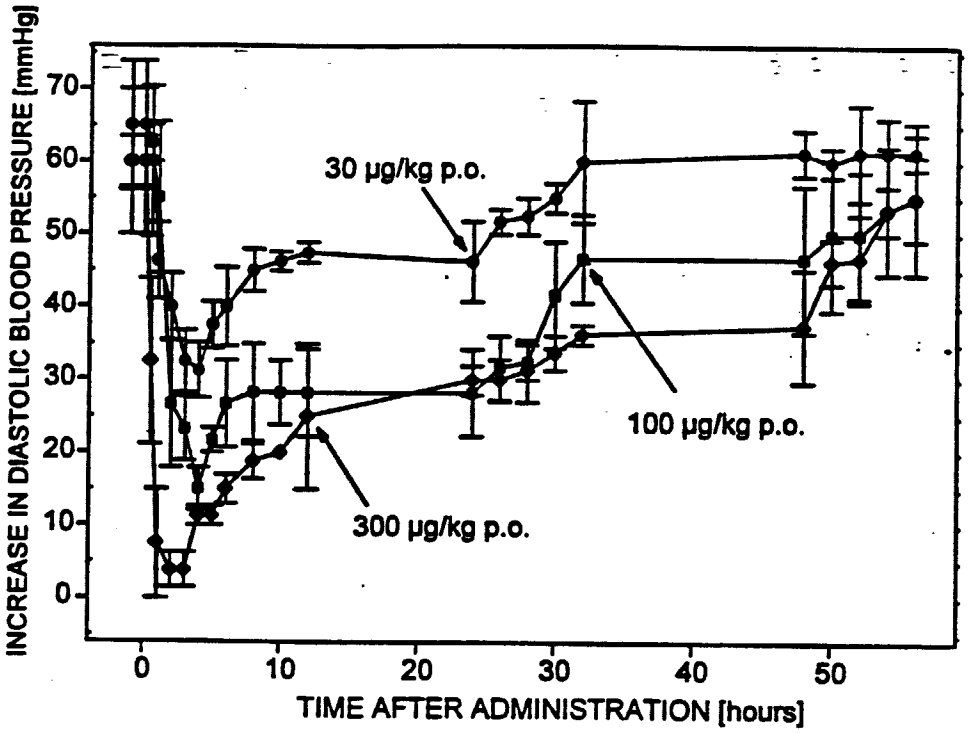


Fig. 1.1.6.: Time course of the angiotensin II blocking effects of telmisartan in conscious dogs after oral administration, showing the increase in diastolic blood pressure induced by repeated iv injection of a bolus of 0.3 µg/kg angiotensin II versus time after administration of telmisartan. Mean ± SEM

The results thus indicate that telmisartan is a potent antagonist of the antihypertensive effect of angiotensin II in conscious dogs. The duration of action is about 1 day after i.v. and 1 to 2 days after oral administration.

1.1.2.4. Studies in Male Cynomolgus Monkeys

This study examined the hypotensive efficacy of telmisartan after oral and i.v. administration in the conscious, sodium-depleted cynomolgus primate. Animals were surgically implanted with a femoral intraarterial catheter, the tip of which was positioned in the abdominal aorta for recording arterial pressure. After a recovery period of 3 weeks, monkeys were trained to sit quietly in restraining chairs and b.p. was recorded in conscious state. Starting one week before experimentation, monkeys were placed on a low-sodium diet, supplemented with fruit. Animals were also injected with furosemide, 3 mg/kg, i.m., 40 hr and 16 hr prior to the experiment.

Telmisartan (0.3 to 10 mg/kg, p.o.) significantly decreased (up to 30-35%) mean arterial pressure without any effect on heart rate. The onset of the hypotensive effect was between 15 and 30 min, with the maximal effect reached by 60-75 min and sustained for at least 3.5 hr (Fig. 1.1.7). Oral dosing was typically associated with dose- and time-dependent increases in plasma renin activity (PRA) and plasma levels of angiotensin II. The increase in PRA was observed with the no hypotensive effect dose of telmisartan (0.1 mg/kg, p.o.), suggesting that a fall in b.p. *per se* need not be required for elevations in PRA following dosing with an angiotensin II receptor antagonist. In other words, the increased levels of PRA may be a consequence of blocking

angiotensin II receptors in renin-secreting tissue (e.g. macula densa). In this model losartan produced a comparable decrease in b.p. at 30 mg/kg.

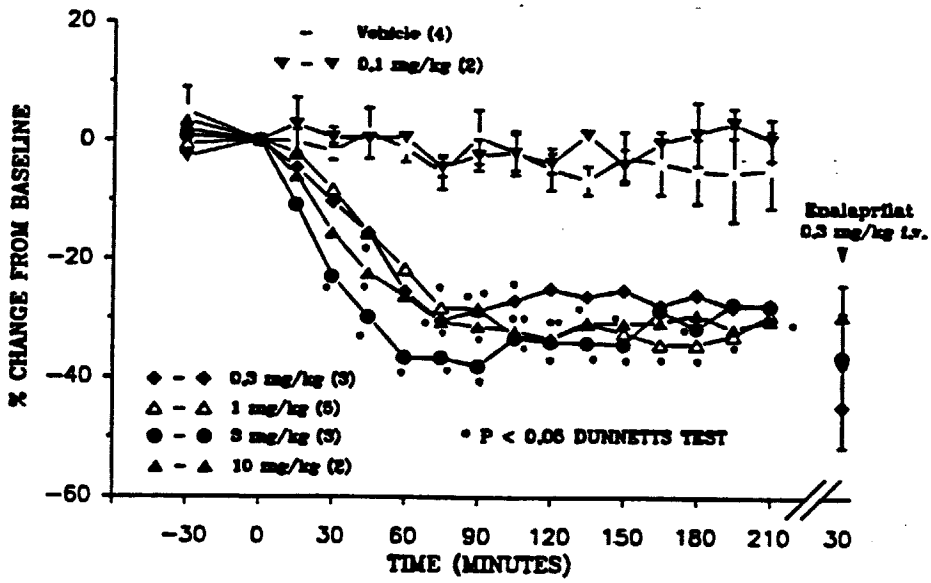


Fig. 1.1.7.: The effect of telmisartan (0.1 to 10.0 mg/kg p.o.) on mean arterial blood pressure in conscious, sodium-depleted cynomolgus monkeys. Plotted values are means ± SEM with the number of experiments in parenthesis. Starting mean arterial pressures were approximately 100 mmHg. Enalaprilat (0.3 mg/kg iv) was administered at the 210 minute time point in all monkeys.

In a related study, duration of the hypotensive effect of telmisartan and its correlation to PRA and plasma levels of angiotensin II were evaluated after oral (1 mg/kg) or i.v. (1 mg/kg) administration in conscious, sodium-depleted monkeys. Telmisartan, at 1 mg/kg p.o., significantly decreased (up to 35%) mean arterial pressure without any significant effect on heart rate. The onset of the hypotensive effect was observed within 1 hr with the maximum effect reached 2 hr post-dose. The effect remained unchanged, up to 7 hr post-dose. Mean arterial pressure was still depressed (26 ± 5%), but not significantly, at 8 hr post- administration (Fig. 1.1.8). Oral administration of telmisartan was associated with significant increases in both PRA and plasma levels of angiotensin II. The increases were apparent at both 24 and 48 hr post-dosing, the time at which the b.p. was nearing normal.

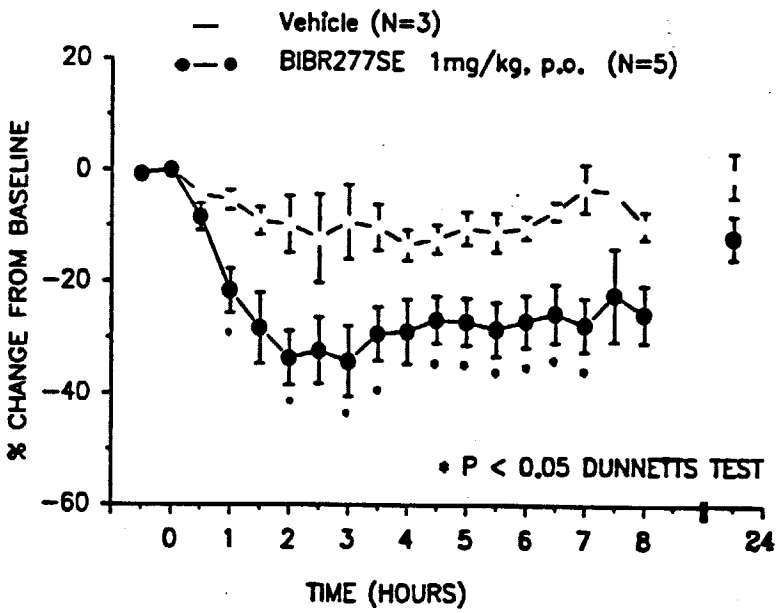


Fig. 1.1.8.: The effect of telmisartan, 1.0 mg/kg p.o. on mean arterial blood pressure over a 24 hour period in conscious, sodium-depleted cynomolgus monkeys. Values are means±SEM with the number of experiments in parenthesis. Starting mean arterial blood pressures were approximately 100 mmHg.

After i.v. dosing, telmisartan significantly decreased mean b.p., with an onset of 5 min, reaching a peak decrease of 42 ± 8% at 1 hr post-dose. The decrease was significant for up to 8 hr post-dosing. The hypotensive effect at 24 hr was modest (11 ± 2%), but statistically significant (Fig. 1.1.9). There was no significant effect on heart rate. As with oral dosing, telmisartan caused increases in PRA and plasma levels of angiotensin II, both during the initial 8 hr as well as at the 24 and 48 hr time points. Thus, both routes of administration lower mean arterial b.p. with long duration and are associated with elevations in PRA and plasma angiotensin II which appear to persist as b.p. returns to near control values.

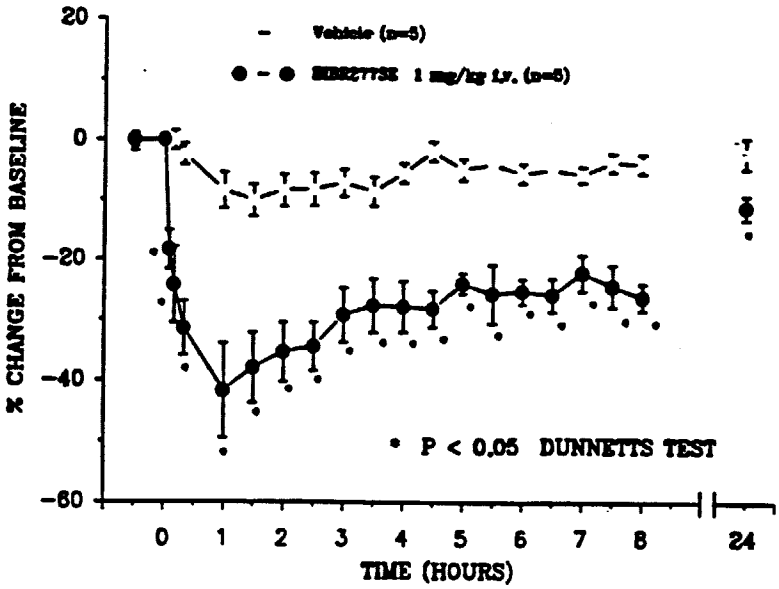


Fig. 1.1.9.: The effect of telmisartan 1.0 mg/kg i.v on mean arterial blood pressure over a 24 hour period in conscious, sodium-depleted cynomolgus monkeys. Values are means±SEM with the number of experiments in parenthesis. Starting mean arterial blood pressures were approximately 100 mmHg.

1.1.2.4. Studies in Marmosets

The inhibition of the angiotensin II pressor response and the duration of action of telmisartan were studied after i.v. administration to anesthetized marmosets.

Marmosets (male and female) fasted overnight were anesthetized by pentobarbital. Carotid artery and jugular veins were cannulated for arterial pressure measurements and drug administration, respectively. After achieving a stable baseline mean arterial blood pressure (MAP), angiotensin II (0.3 μg/kg, i.v. bolus) was administered leaving 10 min between two administrations. When b.p. returned to baseline after the second angiotensin II pressor response, animals received telmisartan 0.3 mg/kg as a single i.v. bolus dose. The animals were challenged with angiotensin II at 5 and 15 min and then every 15 min for 180 min. Intravenous bolus administration of angiotensin II (0.3 μg/kg) increased MAP between 51 and 59 mm Hg from the baseline prior to administration of test drugs. The angiotensin II pressor response was effectively inhibited by telmisartan in a time-dependent manner. The following table summarizes percentage inhibition of angiotensin II response by telmisartan as a function of time.

Time (min)	5	15	30	45	60	75	90	105	120	135	150	165	180
% inhibition	85	76	65	59	49	46	42	42	38	32	26	18	15

1.2. General Pharmacology (Secondary Activities)

1.2.1. *In Vitro*

1.2.1.1. Effects on Enzymes

The possible interference of telmisartan with components of the human renin angiotensin system was determined in enzymatic assays. The renin activity in human plasma was not affected by 10 μM telmisartan whereas it was potently attenuated by the renin inhibitor H142 (0.1 μM). Additionally, telmisartan (10 μM) did not affect the activity of human serum ACE, whereas ACE was decreased 16.4% of control values in the presence of 1 μM captopril.

Telmisartan was a weak inhibitor of both crude (IC_{50}: 54 ± 5 μM) and purified isozymes (range of IC_{50}: 23 to 48 μM) of cAMP-phosphodiesterase prepared from pig left ventricle. Higher concentrations were required to inhibit crude cGMP-phosphodiesterase, although the IC_{50} against cGMP-PDE-I was found to be 24 ± 2 μM. Based on these findings the sponsor concludes that therapeutic doses of telmisartan would not be anticipated to result in blood levels sufficient to inhibit phosphodiesterase.

1.2.1.1. Effects on Renal Function

Effects on Isolated Kidney: This study investigated the effect of telmisartan on renal perfusate flow, urinary flow, and glomerular filtration rate in the isolated, constant pressure (105 mmHg) perfused rat kidney. Test drug was infused in a cumulative fashion at final concentrations of 10, 100 and 1000 nM from 60 to 75, 75 to 90 and 90 to 105 min, respectively. Urine samples were collected for 10 min periods from the 50-60th min, 65-75th min, 80-90th min and 95-105th min for clearance measurements and determination of urinary flow. The time-matched control group received the solvent during the entire experimental period. Cumulative administration of telmisartan resulted in a concentration-dependent and significant increase of all three parameters measured (Table 1.2.1.1). The effects of telmisartan were not dependent on intrarenal stimulation of vasoactive prostaglandins, since in additional experiments the cyclooxygenase inhibitor indomethacin (10 μM) did not inhibit the increase in renal perfusate flow, urinary flow, and glomerular filtration rate after cumulative infusion of telmisartan. This suggests that telmisartan caused renal vasodilation although the kidneys were not preconstricted by angiotensin II. A possible mechanism of action of telmisartan is that it inhibits the vasoconstrictive effect of intrarenally generated angiotensin II on afferent and/or efferent arterioles.

Additional experiments demonstrated that telmisartan (0.1 and 1 μM) was able to further increase the diuretic action of furosemide in the same model. Furosemide increased urinary flow to about 140% of control. Renal perfusate flow also increased modestly but significantly, whereas the glomerular filtration rate remained unaffected. The combined administration of furosemide (10 μM) and telmisartan (0.1 and 1 μM) further increased renal perfusate flow and urinary flow and also significantly increased glomerular filtration rate (Table 1.2.1.2). In contrast, captopril (0.1, 1 μM) did not show potentiation of furosemide-induced diuresis in this model. The findings suggest that telmisartan has an additive effect on furosemide-induced increases in renal perfusate and urinary flow and additionally improves glomerular filtration rate

in the isolated rat kidney. It could be interpreted that these effects are mediated *via* the selective inhibition of glomerular and/or tubular angiotensin II receptors.

TABLE 1.2.1.1
EFFECT OF THE VEHICLE OR CUMULATIVE (10 nM, 100 nM, 1000 nM) INFUSION OF TELMISARTAN ON RENAL PERFUSATE FLOW (RPF), URINARY FLOW (URINE) AND GLOMERULAR FILTRATION RATE (GFR) OF ISOLATED RAT KIDNEY PERFUSED AT CONSTANT PRESSURE.
All values are given as the mean ± SEM of 8 experiments in each group

Group Vehicle/Telmisartan Sample collection period [min]		A control (vehicle) 50' - 60'	B vehicle or 10 nM 65' – 75'	C vehicle or 100 nM 80' – 90'	D vehicle or 1000 nM 95' - 105'
RPF [ml/min*gwwt]	control telmisartan	9.8 ± 0.5 10.7 ± 0.4[n.s.]	9.8 ± 0.5 11.5 ± 0.5[$]	9.8 ± 0.5 11.9 ± 0.4[$]	9.6 ± 0.6 12.3 ± 0.5[$]
Urine µl/min*g wwt	control telmisartan	96.0 ± 6 88.0 ± 6[n.s.]	99.0 ± 6 97.0 ± 6[$]	99.0 ± 7 108.0 ± 8[$]	96.0 ± 9 114.0 ± 8[$]
GFR [µ/min*gwwt]	control telmisartan	513.0 ± 29 513.0 ± 25[n.s.]	474.0 ± 32 530.0 ± 27	434.0 ± 31[$] 554.0 ± 27[$]	403.0 ± 38[$] 574.0 ± 30[$]

[$]: Statistically significant difference from the initial value in interval A (50' - 60') within each group.
n.s.: No statistically significant differences between the control and the telmisartan-treated group
wwt: Wet weight

TABLE 1.2.1.2
EFFECT OF CUMULATIVE INFUSION OF TELMISARTAN (0.1 AND 1.0 µM) IN THE PRESENCE OF FUROSEMIDE (10 mM) ON RENAL PERFUSATE FLOW (RPF), URINARY FLOW (URINE) AND GLOMERULAR FILTRATION RATE (GRF) OF ISOLATED RAT KIDNEYS.
All values are given as the mean ± SEM of 8 experiments.

Group Vehicle/Treatment(s) Sample collection period [min]	A control (vehicle) 50' - 60'	B furosemide (10mM) 65' - 75'	C +10mM furosemide +0.1µM telmisartan 80' - 90'	D +10mM furosemide + 1µM telmisartan 95' - 105'
RPF [ml/min*g_{wwt}]	9.4 ± 0.7	9.9 ± 0.8[$]	10.7 ± 0.7[$§]	11.2 ± 0.7[$§]
urine [ml/min*g_{wwt}]	91.0 ± 7	126.0 ± 7[$]	161.0 ± 9[$§]	182.0 ± 9[$§]
GFR [ml/min*g_{wwt}]	480.0 ± 16	487.0 ± 17	530.0 ± 18[$§]	560.0 ± 20[$§]

[$] denotes P<0.05 from the initial control value in interval A (50' - 60')
[§] denotes P<0.05 from value in interval B (65' - 75') in the presence of furosemide

1.2.2. *In Vivo*

1.2.2.1. Effects on Renal Function

A. Rats: The acute effect on renal function after i.v. administration of telmisartan (0.1, 0.3, and 1 mg/kg bolus) was investigated in normotensive, anesthetized male rats. Telmisartan had no effect on b.p. at 0.1 mg/kg. At 0.3 mg/kg, it decreased mean diastolic b.p. slightly, but significantly, at 20, 40 and 60 min postdose. A persistent significant decrease in diastolic b.p. was observed at a dose of 1 mg/kg (Fig. 1.2.2.1). No significant effects on heart rate were observed with any doses.

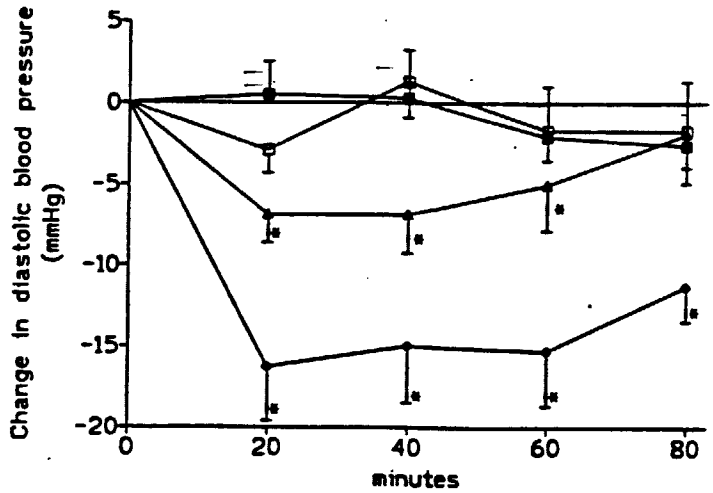


Fig. 1.2.2.1.: Effect of telmisartan (iv - bolus) or vehicle on diastolic blood pressure of anaesthetized rats. Filled squares: vehicle (n = 10); open squares: 0.1 mg/kg (n = 10); open triangles: 0.3 mg/kg (10); open diamonds: 1 mg/kg (6); values as mean ± SE; * p<0.05 vs predrug-value

In the same study, telmisartan increased cumulative urine production (Fig. 1.2.2.2) and sodium excretion (Fig. 1.2.2.3) at 0.1 and 0.3 mg/kg, the effect being significant at 0.3 mg/kg. However, at the highest dose no increase in either urinary flow and sodium excretion was observed, indicating that diuresis and natriuresis is critically dependent on blood pressure. Thus the lack of a diuretic and saluretic effect at the high dose might be explained by a drop in renal perfusion pressure and/or the selective dilation of the efferent arterioles. Both effects would result in a decrease in effective filtration pressure, glomerular filtration rate and hence filtrate fraction. The study also demonstrated that telmisartan has no effect on potassium excretion (figure not shown).

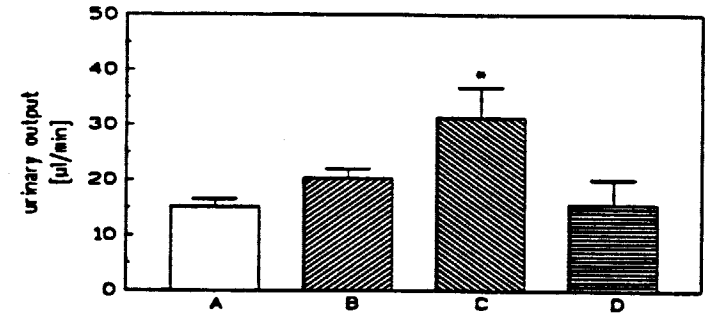


Fig. 1.2.2.2.: Effect of intravenous administration of telmisartan or its vehicle on urinary output in anaesthetized rats. Column A: vehicle (n = 10); column B: 0.1 mg/kg (n=10); column C: 0.3 mg/kg (n = 10); column D: 1 mg/kg (n = 6); values as mean ± SE; * p<0.05 vs control.

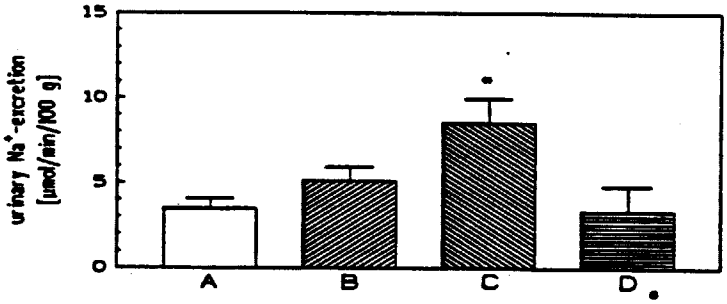


Fig. 1.2.2.3.: Effect of intravenous administration of telmisartan or its vehicle on Na^+-excretion in anaesthetized rats. Column A: vehicle (n = 10); column B: 0.1 mg/kg (n = 10); column C: 0.3 mg/kg (n = 10); column D: 1 mg/kg (n = 6); values as mean ± SE; * p<0.05 vs control

The effect of sodium loading via the drinking water on blood urea nitrogen (BUN) and plasma creatinine after oral administration of telmisartan (50 mg/kg/day) for two weeks was investigated in normotensive male and female rats [ ] The animals were divided into four groups as indicated in table 1.2.2.1. No significant differences could be detected for either parameter between the normal and the sodium loaded rats. The plasma levels of BUN and creatinine after 14 days of treatment were significantly increased in the telmisartan-treated group without salt supplementation (Table 1.2.2.1). In contrast, additional salt intake (group 4) completely prevented the increase in BUN and creatinine during treatment with telmisartan. The findings suggest that angiotensin II receptor blockade, resulting in vasodilation of efferent arterioles in the kidney, leads to a decrease in glomerular pressure and hence, in glomerular filtration rate. Effective urea absorption in the tubules would increase due to the decrease in urine flow in tubules. As a consequence of this increase in urea absorption from the tubules and the increase in renal blood flow due to renal vasodilation, BUN would increase during treatment. A positive sodium balance would lead to a down-regulation of the RAAS in these animals and prevent the renal effects of angiotensin II receptor blockade after administration of a high dose of telmisartan.

TABLE 1.2.2.1

BLOOD UREA NITROGEN (BUN) AND PLASMA CREATININE AFTER 14 DAYS OF TREATMENT WITH EITHER VEHICLE (0.5% NATROSOL SUSPENSION) OR TELMISARTAN (50 MG/KG/DAY) IN NORMAL (GROUP 1 AND 2) AND SODIUM-LOADED (GROUP 3 AND 4) RATS.

Values are Mean ± SD of 6, 5, 6, and 6 animals/group, respectively

	Group 1 tap-water + vehicle	Group 2 tap-water + telmisartan	Group 3 0.9% saline + vehicle	Group 4 0.9% saline + telmisartan
BUN (mmol/l)	9 ± 1	19.6 ± 2.2*#	8.9 ± 0.3	8.5 ± 0.9
Ceatinine (µmol/l)	52.0 ± 5	59.0 ± 8$	49.0 ± 5	47.0 ± 4

* $p < 0.01$ group 2 vs group 1
\# $p < 0.01$ group 2 vs group 3
§ $p < 0.01$ group 2 vs group 4
$ $p < 0.05$ group 2 vs group 4

B. Dogs: The acute effect on renal function after i.v. administration of telmisartan (0.03, 0.1 and 0.3 mg/kg bolus) was studied in conscious female beagle dogs (n=8/dose). Each dog received the vehicle or drug on 4 different days. Three months before the study dogs were ovarectomized and episitomized. On the day of the experiment, bladder catheters were inserted and urine was collected before (-2 to 0 hr) and at 2 and 6 hours after drug or vehicle administration (saline, 0.2 ml/kg). From each sample, urine volume and concentrations of creatinine, Na^+, K^+ and Cl^- were determined.

Telmisartan increased excretion of water, Na^+ and chloride at all dose levels, the effect being maximum at 0.1mg/kg (3, 6 and 3.5 times the control, respectively). These data confirm the previous results obtained in the anesthetized rats (see above). The diuretic effects of telmisartan is partly explained by an increased glomerular filtration rate due to the blockade of vascular angiotensin AT_1 receptors in the kidneys. Excretion of K^+ and creatinine were not changed by test compound. In contrast, classical diuretics like hydrochlorothiazide and furosemide promote K^+ excretion. Since telmisartan does not inhibit the release of aldosterone, the "K^+ sparing" effects of telmisartan may be related to additional mechanisms, possibly not related to angiotensin receptor blockade.

1.2.2.2. Effects on Other Systems

Telmisartan showed low acute toxicity during cumulative infusion into anesthetized guinea pigs. Lethal doses (i.e. cardiac arrest) ranged from 193 to 247 mg/kg, when the compound was infused at a rate of 3.33 mg/kg/min. A positive inotropic effect occurred at doses far beyond the anticipated therapeutic range.

Telmisartan (1 mg/kg, i.v.), unlike captopril (1 mg/kg, i.v.), did not potentiate bradykinin (1 μg/kg/min)-induced bronchoconstriction in anesthetized guinea pigs.

The potential effect of telmisartan on the central nervous system was studied in rats and mice. Test compound, at 30 mg/kg p.o., did not influence spontaneous motor activity of conscious freely moving rats or hexobarbital-induced sleeping time in rats at up to 1 hour post-administration. Telmisartan (30 mg/kg, p.o.) also failed to cause muscle relaxation in mice up to 2 hours post administration. The findings suggest that telmisartan does not act on the CNS and that there is no effect on drug metabolizing enzymes of liver (hexobarbital metabolized by liver).

In other studies, telmisartan (10 and 30 mg/kg p.o.) showed no effect on the distribution of a barium meal along the intestine in conscious rats, indicative of lack of effect on intestinal propulsion in this model. Also, telmisartan (10 and 30 mg/kg p.o.) failed to affect gastric emptying of an Altromin (mush) meal, during a 1 hour period, in conscious rats. These results suggest that doses as high as 30 mg/kg of telmisartan have no effect on gastrointestinal motility.

2. DRUG DISPOSITION (ADME)

Pharmacokinetic data analysis: Abbreviations used in the study summaries

AUC	[µg.h/ml]	= AUC in general
AUC_{0-tf}	[µg.h/ml]	= area under the plasma drug concentration-time curve within the interval from zero to time t_f
AUC_{0-tf}	[µg-eqv.h/ml]	= area under the plasma concentration-time curve of radioactivity within the interval from zero time to t_f
$AUC_{tf-\infty}$	(%)	= the percentage of extrapolated area under the curve from calculated t_f to infinity is defined as $AUC_{tf-\infty} / AUC_{0-\infty} \times 100$
$AUC_{0-\infty}$	[µg-eqv.h/ml]	= area under the plasma concentration-time curve of radioactivity from zero time to infinity, i.e., $AUC_{0-\infty} = AUC_{0-tf} + C(t_f) / \lambda_z$
AUC_{0-5h}	[µg.h/ml]	= area under the blood concentration-time curve of radioactivity from zero to time to t = 5 h
AUC_{0-24h}	[µg.h/ml]	= area under the plasma drug concentration-time curve of radioactivity from zero to time to t = 24 h
Cmax	[µg/ml]	= maximum concentration of drug in plasma
Cmax	[µg-eqv/ml]	= maximum concentration of radioactivity in plasma
$C_{5\,min}$	[µg/ml]	= concentration of drug in plasma at time = 5 min after the end of bolus injection
C_0	[µg/ml]	= concentration of drug in plasma at time zero, extrapolated from the 0.083 to 0.25h values using a linear function
$C_{0\,norm}$		= relative concentration of drug in plasma at time zero, normalized to the concentration after 1 mg/kg.
Cl_{tot}	[ml/min/kg]	= total clearance
$C(t_f)$	[µ00g/ml]	= calculated concentration at t_f using the regression equation
$CL_{tot/f}$	[(ml/min)/kg]	= total clearance of drug or radioactivity from plasma
CV	(%)	= coefficient of variation
E_i		= 1 - (AUC_{id}/AUC_{ipv}) intestinal extraction ratio
E_h		= 1 - (AUC_{ipv}/AUC_{iv}) hepatic extraction ratio
E_t		= 1 - (AUC_{id}/AUC_{iv}) total extraction ratio
f	[none]	= bioavailability factor
λ_z	[1/h]	= terminal elimination constant, equal to the regression coefficient b of the log-linear regression line ln C = a + b . t of the final 3 - 4 data points above the quantitation limit
MRT_{tot}	[h]	= total mean residence time (0-∞) of parent compound
t_{max}	[h]	= time to maximum concentration
t_f	[h]	= time of the final data point above the quantitation limit
$t_{½}$	[h]	= terminal half-life
TCG	[h]	= for total radioactivity: the time coordinate for the center of gravity corresponding to MRT_{tot}
V_{ss}		= volume of distribution in steady state regression coefficient b of the log-linear regression line ln C = a + b.t of the final 2 - 4 data points above the quantitation limit
V_{app}		= apparent volume of distribution calculated as the quotient dose /C_0
V_c	[l/kg]	= apparent volume of distribution of the central or plasma compartment after i.v.
V_z/f	[l/kg]	= apparent volume of distribution during the terminal λ_z phase
V_{ss}/f	[l/kg]	= volume of distribution (apparent) under steady-state conditions based on radioactivity or drug concentration in plasma

2.1. Absorption and Pharmacokinetics

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

This non GLP study was conducted by[ ] between April and July 1994. The objective of the study was to determine the basic pharmacokinetics and excretion of the administered radioactivity in male and female mice.

The dosage was 1 mg/kg [^{14}C]telmisartan (batch #Br 872/26) administered orally by gavage and i.v. by bolus injection into the tail vein (volume in both cases 10 ml/kg). The weights of the 0F1 mice used in this study were in the range of 19-36 gm. The animals were fasted for 16 hr and were fed 1 hr after the administration of test substance. Test substance was dissolved in 0.5 N NaOH. The preparation was diluted with normal saline and the pH was adjusted to 8-9 with 0.5 N HCl. The concentration was 0.1 mg/ml for both p.o. and i.v. administration.

The experimental groups and investigations performed are shown in the following table.

Group	Route of administration	N (M/F)	Sampling matrix	Investigation performed
1	Intravenous	40 M	Plasma	Radioactivity, Telmisartan
2	Intravenous	40 F	Plasma	Radioactivity, Telmisartan
3	Oral	40 M	Plasma	Radioactivity, Telmisartan
4	Oral	40 F	Plasma	Radioactivity, Telmisartan
5	Oral	10 M	Urine, feces	Radioactivity
6	Oral	10 F	Urine, feces	Radioactivity

Levels of total radioactivity and parent compound[ ] analysis) were determined in blood/plasma collected from the retroorbital venous plexus from 5 animals/sex/sampling point/route. Samples were collected at: 0.5, 1, 2, 4, 6, 8, 24 and 48 hr after oral and 0.083, 0.5, 1, 2, 4, 8, 24 and 48 hr after i.v. administrations. Excretion of [^{14}C]telmisartan was determined by measuring radioactivity present in urine and feces only in animals dosed orally. Urine samples were collected at 0-3, 3-6, 6-24, 24-48 and 48-72 hr after oral dosing. Feces were collected as 24 hr fractions up to 72 hr).

Results

After oral administration of 1 mg/kg [^{14}C]telmisartan, peak plasma levels of radioactivity and of parent compound were attained at 2 hr. After i.v. administration, peak blood levels were reached at the first time point (0.083 hr). The terminal elimination half-lives after oral and i.v. dosing were between 8 and 10 hr (Table 2.1.1.1). The extent of absorption, as calculated on the basis of AUC values derived from blood concentration-time profiles of radioactivity, was 82% for males and 62% for females; the absolute bioavailability was 75% for males and 56% for females.

TABLE 2.1.1.1
MEAN CONCENTRATION-TIME PROFILES OF RADIOACTIVITY AND PARENT COMPOUND AFTER ORAL AND I.V. ADMINISTRATION OF 1 MG/KG [^{14}C] TELMISARTAN TO MALE AND FEMALE MICE

Parameter	Radioactivity				Parent compound			
	Intravenous		Oral		Intravenous		Oral	
	males	females	males	females	males	females	Males	females
C_{max} [ng-eqv/ml]	552	581	183	238	498	480	134	190
T_{max} [hour]	0.083*	0.083*	2.0	2.0	0.083*	0.083*	2.0	2.0
$t_{1/2}$ [hour]	9.5	8.5	10.1	8.4	8.7	7.0	7.3	6.3
$AUC_{0-\infty}$ [ng-eqv·h/ml]	2180	3272	1787	2019	1678	2612	1256	1473
TCG [hour]	12	11	13	11	-	-	-	-
MRT_{tot}[hour]					10	8.7	10	9.1
Cl_{tot}[ml/min/kg]					10	6.4	-	-
V_{ss}[l /kg]					5.9	3.3	-	-
F	-	-	0.82**	0.62**	-	-	0.75**	0.56**

* first time point
** calculated on the basis of rounded values

For the parent compound, the concentration-time profile was comparable to the profile for radioactivity. A comparative analysis of the results obtained from plasma samples using

following oral administration showed that 70-80% of the radioactivity was represented by parent compound up to 8 hours. At 24 and 48 hours after oral dosing only 60% of the radioactivity was represented by the parent compound. After intravenous dosing, over 80% of the drug appeared as the parent compound in the plasma. There was no difference in total radioactivity in the plasma samples from males and females following oral administration. However, for the parent compound, a higher maximum concentration (C_{max}) was observed in females as compared to males ($P \leq 0.05$). After intravenous injection, higher plasma concentrations of radioactivity and of parent compound were observed at all time points (α = 0.05 significance level) in females compared to males. The volume of distribution at steady state was large (3-6 L/kg), indicating a preferential distribution into the tissue.

After oral administration the radioactivity was excreted predominantly (87/85%, females/males) by the fecal route; only 1-4% was detected in urine. The bulk of radioactivity (~ 60%) was excreted within the first 24 hours after dosing. Mean total excretion was incomplete at 72 hr after oral administration (Table 2.1.1.2). The excretion of radioactivity in the bile is detailed in section 2.4.1.

TABLE 2.1.1.2

CUMULATIVE EXCRETION OF TOTAL RADIOACTIVITY (% OF THE DOSE ADMINISTERED) AFTER SINGLE ORAL ADMINISTRATION OF 1 MG/KG [^{14}C]TELMISARTAN TO MICE (N=10/TIME POINT)

Time (hr)	Male			Female		
	Urine + Cage wash	Feces	Total excretion	Urine + Cage wash	Feces	Total excretion
0-3	0.3			0.04		
0-6	1.3			0.2		
0-24	2.8	58.1	60.9	0.6	60.9	61.4
0-48	3.7	77.9	81.7	0.8	80.2	81.0
0-72	4.0	85.2	89.2	1.1	87.0	88.1

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

This non GLP study was conducted by in November/December 1991. The objective of the study was to determine the basic pharmacokinetics and tissue distribution in male rats and record the metabolite pattern from the bile.

The dosage in general was 1 mg/kg [^{14}C]telmisartan (batch #Ei 4465 and KS 123/5) administered orally by gavage and i.v. by bolus injection. However, in the whole-body autoradiography experiment 10 mg/kg was used because of the low specific radioactivity of the substance. The weights of the rats used for whole-body autoradiography were in the range of 160-170 gm. The rest of the rats weighed between 220 and 240 gm. The animals were fasted for 20 hr and were fed 2 hr after the administration of test substance. The animals that were used for the whole-body autoradiography were not fed after the administration of test substance. Test substance was dissolved by brief sonication in absolute ethanol and 1 N NaOH. The preparation was diluted with normal saline and the pH was adjusted to 7-8 with 0.1 N HCl. The concentration was 0.5 mg/ml for the intravenous and 0.25 mg/ml for the oral administration. Solutions with 4 and 2 mg/ml were prepared for the whole-body autoradiography. Telmisartan solution was administered into the caudal vein or with a stomach tube into the stomach. Total radioactivity was determined in blood (at different intervals from 0.08 to 48 hr), plasma, urine (0-8, 8-24, 24-48, 48-72 and 72-96 hr) and feces (collected in 24 hr fractions up to 96 hr) (n=5 rats/route). In the whole-body autoradiography experiment, the animals were sacrificed by anesthesia at different times after test substance administration and after collection of blood samples. The animals were deep frozen and 30 μm thick serial sections were obtained at different levels of anatomical interest.

In another group of five rats, biliary excretion of test substance was studied by inserting a cannula into the bile duct with bile collected in fractions at various intervals. Enterohepatic cycling of [^{14}C]telmisartan was investigated by intraduodenal administration of 1 ml bile collected from donor animals (n=5). The donor animals had received test drug i.d. (1 mg/kg) on the previous day and the bile was collected ice cold, unfractionated from 0-6 hr (stored at 4 C).

Results

After oral administration of 1 mg/kg [^{14}C]telmisartan, plasma concentration-time curves showed a biphasic profile with the first (major) peak at 2 hr (range 0.5 to 6 hr) and the second (minor) peak between 4 and 12 hr after administration, suggesting enterohepatic cycling of parent compound (see below). After i.v. administration, peak blood levels were reached at the first time point (0.08 hr). The terminal elimination half-lives after oral and i.v. dosing were about 7 and 6.5 hr, respectively (Table 2.1.2.1). From the areas under the blood level curves up to 24 hr after oral and i.v. administration, an absolute bioavailability of of 67% was estimated. Regarding the distribution of radioactivity, most of the ^{14}C was distributed in the plasma. The ratio of concentration in the solid parts of the blood (C_E) to concentration in the plasma (C_P) varied between 0.02 and 0.19 throughout the study period.

TABLE 2.1.2.1
PHARMACOKINETIC PARAMETERS IN BLOOD AFTER ORAL AND I.V. ADMINISTRATION OF 1 MG/KG [^{14}C]TELMISARTAN TO MALE RATS (N=5)

Parameter	Unit	Radioactivity	
		Oral	Intravenous
C_{max}	[µg-eqv/ml]	0.0529	0.577
T_{max}	[h]	2.00	
$AUC_{0-\infty}$	[µg-eqv·h/ml]	0.732	1.144
MRT_{tot}	[h]	10.7	6.01
$t_{½}$	[h]	7.00	6.52
CL	[ml/min/kg]	24.0	14.6
F_a (AUC)[1]			0.67

[1]: fraction of drug absorbed, $AUC_{p.o.}/AUC_{i.v.}$

The radioactivity was eliminated almost completely via the feces (99.5%) and elimination was essentially completed 72 hr after administration. The fraction eliminated renally after oral and i.v. administration was approximately 0.1% (Table 2.1.2.2). The radioactivity administered was excreted almost exclusively via the bile. About 57% and 83%, respectively, of the administered radioactivity was excreted with the bile within 6 hr after intraduodenal and i.v. adminstration of [^{14}C]telmisartan (Fig. 2.1.2.1). After the i.d. administration of donor bile, the enterohepatic circulation of [^{14}C]telmisartan starts slowly. However, it increases constantly so that 10% of the administered radioactivity has been excreted 6 hr post-dose (see Fig. 2.1.2.1 e.h.c. curve).

TABLE 2.1.2.2
CUMULATIVE EXCRETION OF TOTAL RADIOACTIVITY (% OF THE DOSE ADMINISTERED) AFTER SINGLE ORAL OR I.V. ADMINISTRATION OF 1 MG/KG [^{14}C]TELMISARTAN TO MALE RATS (N=5)

Time (hr)	Oral			Intravenous		
	Urine + Cage wash	Feces	Total excretion	Urine + Cage wash	Feces	Total excretion
0-8	0.03	ND	ND	0.05	ND	ND
0-24	0.07	84.29	84.35	0.10	85.11	85.20
0-48	0.07	98.42	98.50	0.11	98.25	98.36
0-72	0.08	99.50	99.58	0.11	99.35	99.46
0-96	0.08	99.65	99.73	0.12	99.46	99.58
AUC_{0-96}	6.38	7968.80	7975.10	9.19	7978.30	7987.40

ND: not determined

A comparison of the concentration-time profiles of total radioactivity in blood and the parent compound in plasma indicated that after oral administration mainly parent substance circulates in the blood. This confirms that the carrier of the pharmacodynamic action is practically exclusively telmisartan. No significant amounts of metabolites were present in the circulation. The radioactivity found in the bile was in the form of a glucuronide and /or a sulfate of the parent compound.

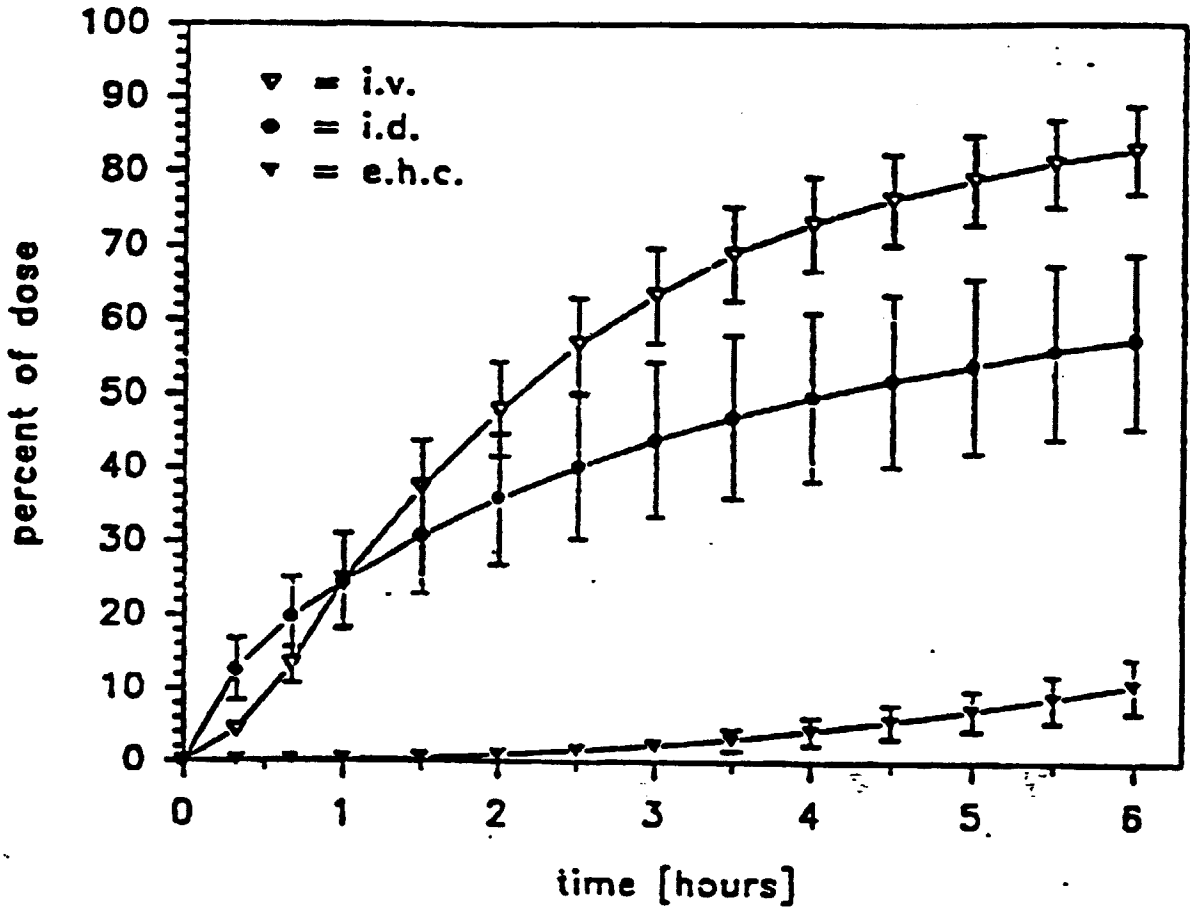


Fig. 2.1.2.1.: Cumulative biliary excretion and enterohepatic cycling (e.h.c.) of total radioactivity after i.v. and i.d. administration of labeled drug.

Measurements of the concentration of the radioactivity in the tissues and of the contemporary whole-body autoradiograms showed that after i.v. administration the radioactivity was distributed in the entire organism. Five minutes after i.v. administration, high concentrations of radiolabelled material were present in blood, liver, lung, adrenal, kidney and myocardium. The very high concentration in the liver indicates a marked elimination of the radioactivity with the bile. Eight hours after administration, elimination had progressed so far that high substance concentrations were found only in the intestinal tract and the liver. The CNS showed very little radioactivity at all times. Other organs showed practically no radioactivity. Radioactive distribution 5 min after oral administration was similar to that 5 min after i.v. administration;

radioactivity concentrations 5 min after p.o. adminsitration were, however, lower and at 8 hr the tissue levels were slightly higher compared with the i.v. value (Table 2.1.2.3).

TABLE 2.1.2.3
TISSUE CONCENTRATION OF THE TOTAL RADIOACTIVITY AFTER INTRAVENOUS AND ORAL ADMINISTRATION OF 10 MG/KG [^{14}C]TELMISARTAN TO MALE RATS

Tissue	Intravenous		Oral	
	0.083 h [ng-eqv/g]	8.0 h [ng-eqv/g]	0.5 h [ng-eqv/g]	8.0 h [ng-eqv/g]
Brain	694	11	75	31
Lungs	16107	232	1968	670
Liver	62161	13830	32661	22892
Muscle	3296	75	389	109
Blood (heart)	17870	272	2419	796
Thymus	3981	63	404	157
Salivary Gland	7820	111	1011	284
Testis	1363	43	191	126
Fat	4971	120		200
Blood (retro.)	22900	272	2726	774
Plasma	39354	469	4138	1280
Erythrocytes	5075	66	854	202
Hematocrit (%)	48	49	43	47
CE/CP (F)	0.13	0.14	0.21	0.16

C_E: concentration in the solid parts of the blood
C_P: concentration in the plasma

2.1.3. Pharmacokinetics of Telmisartan in Rats (Report #B521, Study #U97-2008)

This non GLP study was conducted by

, between September and December 1995. The objective of the study was to determine the dose non-linearity in the pharmacokinetics of telmisartan following three different routes of administration. Additionally, the metabolic pattern and the existence of metabolite(s) were studied.

Male albino rats (strain: SPF) weighing 205 to 245 gm were used. The animals were fasted for 16 hr and were fed 2 hr or 1.5 hr, respectively, after i.d or i.v. administration of test substance. Test substance (batch #8230231) and [^{14}C]telmisartan (batch Br 872/26 and Ag 66/2 (for infusion experiment)) were dissolved in 0.5 M NaOH, neutralized with 0.5 M HCl and adjusted to appropriate concentrations/volume with normal saline. The animals were anesthetized with pentobarbitone sodium (given intraduodenally) before administration of drug. The drug was administered to rats intraduodenally (i.d.), intravenously (as an infusion into the tail vein) or intraportally (as an infusion into the portal vein, i.p.v.) at doses of 1, 10 and 30 mg/kg. The infusion time was about 120 seconds for all administrations with the exception of an hour i.v. and i.p.v. for the 1 mg/kg dose (Table 2.1.3.1).

TABLE 2.1.3.1
COMPOSITION AND IDENTITY OF GROUPS

Dose, mg/kg	Route of admn.	N	Plasma from	Total ^{14}C	Parent compd.	Metabolic
1	i.v.	12	Carotid art.	+	+	+ N=2
1	i.v. (1 h infusion)	9	Carotid art.	+	-	-
1	i.p.v.	12	Carotid art.	+	+	+ N=2
1	i.p.v. (1 h infusion)	6	Carotid art.	+	-	-
1	i.d.	4	Carotid art.	+	+	+ N=2
10	i.v.	4	Carotid art.	+	+	+ N=2
10	i.p.v.	4	Carotid art.	+	+	+ N=2
10	i.d.	4	Carotid art.	+	+	+ N=2
30	i.v.	4	Carotid art.	+	+	+ N=2
30	i.p.v.	4	Carotid art.	+	+	+ N=2
30	i.d.	3	Carotid art.	+	+	+ N=2
1	i.d.	2	v. porte	+		+
30	i.d.	2	v. porte	+		+

Total radioactivity, parent compound and/or metabolite formed were determined in blood/plasma collected either from carotid artery or portal vein under anesthesia (Table 2.1.3.1). Samples were collected at the following time points after administration of test substance.

I.V. administration (bolus): 0.033, 0.117, 0.25. 1.5 and 5 hr.

I.V. administration (1 hr infusion): 0.033, 0.666, 0.950, 1.25, 2, 3 and 5 hr.
I.P.V. administration (bolus): 0.033, 0.117, 0.25. 1.5 and 5 hr.
I.P.V. administration (1 hr infusion): 0.033, 0.666, 0.950, 1.25, 2, 3 and 5 hr.
I.D. administration, blood samples collected from carotid artery/ portal vein: 0.033, 0.117, 0.25. 1.5 and 5 hr.

Blood levels of total radioactivity were quantified in a analyzer, whereas plasma levels of parent compound and the main metabolite were quantified by a specific and sensitive method.

Results

Plasma levels of telmisartan after i.v., i.p.v. and i.d. administration are dose non-linear. This is reflected in the $C_{5\,min}$, $AUC_{0\text{-}5h}$, V_{app} and the MRT values (Table 2.1.3.2). With i.v. and i.p.v. administrations, the blood levels of total radioactivity and plasma levels of parent compound (>90%) were close together, indicating that there are only relatively small amounts of metabolites circulating in the plasma. The extraction ratio ($1\text{-}AUC_{i.p.v.}/AUC_{i.v.}$) is nearly zero (see AUC values in Table 2.1.3.2 and 2.1.3.3). This suggests that the liver did not primarily extract telmisartan from blood. The apparent volume of distribution after i.v. and i.p.v. administrations decreased with the increase in dose but not in a proportional manner.

TABLE 2.1.3.2
PHARMACOKINETIC PARAMETERS CALCULATED FROM RADIOACTIVITY, PARENT COMPOUND AND GLUCURONIDE PLASMA LEVELS AFTER I.V. ADMINISTRATION (BOLUS/INFUSION) OF [^{14}C] TELMISARTAN TO MALE RATS

Parameter	Radioactivity Dose [mg/kg]				Parent compound Dose [mg/kg]			Glucuronide Dose [mg/kg]		
	1**	1	10	30	1	10	30	1	10	30
C_{max} (C_{5min})	0.871	0.8547	34.27	123.0	0.718	31.3	109	0.026	0.373	3.172
t_{max}	0.844	0.088	0.083	0.083	0.083	0.083	0.083	0.118	0.144	0.204
$t_{½}$	2.27	1.697	1.024	0.8110	1.747	1.001	0.8846	0.878	1.340	#
$AUC_{0\text{-}5h}$	1.531	1.088	32.41	163.0	0.9366	28.85	124.1	0.043*	0.346*§	#
$AUC_{0\text{-}\infty}$	1.924	1.231	33.22	166.0	1.069	29.53	126.6	0.049	0.482	#
$AUC_{tf\text{-}\infty}$	18.0	10.86	2.306	1.600	11.8	2.13	1.94	12.840	6.865	#
MRT_{tot}	3.021	2.067	1.041	1.280	2.165	1.022	0.7058	1.243	1.683	#
CL_{tot}	8.660	13.54	5.017	3.010	15.59	5.644	3.949	339.5	346.0	#
V_z	1.701	1.988	0.4449	0.2110	2.358	0.4892	0.3024	25.8	40.1	#
V_{app}	–	857.2	248.9	213.0	1.15	0.279	0.241	45.63	24.7	10.601
V_{ss}	1.297	1.679	0.3134	0.2310	2.025	0.3460	0.1673	25.32	34.93	#

** 1 hr infusion
# Not evaluable due to two values for loglinear regresion only.
* AUC was only calculated from 0 to 2.5 h because of missing 5 h value.
§ The value for C = 2.5 h was calculated with the parameter from the regression line after log transformation.

TABLE 2.1.3.3
PHARMACOKINETIC PARAMETERS CALCULATED FROM RADIOACTIVITY, PARENT COMPOUND AND GLUCURONIDE BLOOD/PLASMA LEVELS AFTER I.P.V. ADMINISTRATION (BOLUS/INFUSION) OF [^{14}C] TELMISARTAN TO MALE RATS

Parameter	Radioactivity Dose [mg/kg]				Parent compound Dose [mg/kg]			Glucuronide Dose [mg/kg]		
	1**	1	10	30	1	10	30	1	10	30
C_{max} (C_{5min})	0.761	1.195	36.85	119.4	0.859	31.7	92.8	0.02	0.30	3.55
t_{max}	0.95	0.083	0.083	0.083	0.083	0.083	0.083	0.12	0.08	0.20
$t_{½}$	2.440	2.074	1.037	1.131	2.222	1.014	1.051	#	0.89	1.07
AUC_{0-5h}	1.298	1.205	34.45	177.6	0.9216	29.99	137.8	#	0.27*	3.37*
$AUC_{0-\infty}$	1.677	1.397	35.42	191.0	1.134	30.75	145.7	#	0.34	4.70
$AUC_{tf-\infty}$	19.4	13.22	2.478	3.965	15.1	2.38	3.35	#	10.97	9.42
MRT_{tot}	3.202	2.181	1.071	1.667	2.519	1.081	1.580	#	1.21	1.54
CL_{tot}	9.941	11.93	4.715	2.618	14.70	5.420	3.433	#	493.65	106.49
V_z	2.098	2.038	0.4232	0.2563	2.815	0.4757	0.3122	#	37.90	9.87
V_{app}	–	551.1	220.8	218.4	0.960	0.265	0.293	25.73§	32.01	15.82
V_{ss}	1.592	1.561	0.3029	0.2618	2.222	0.3514	0.3255	#	35.86	9.83

** 1 hr infusion
# Not evaluable due to two values for loglinear regression only.
§ V_{app} for rat 13 was calculated from time values 0.167 to 0.25 h because of missing values.
* AUC was only calculated from 0 to 2.5 h because of missing 5 h value.

Absorption after i.d. administration (1 mg/kg) was extremely rapid. At 5 min after administration the mean plasma level of parent compound was 0.18 µg/ml and the mean plasma level of total radioactivity was 0.778 µg/ml. The concentration of the glucuronide metabolite (0.658 µg/ml) at this dose was higher than the concentration of the parent compound (Table 2.1.3.4). This indicated that the intestinal wall was the primary organ for the glucuronidation of telmisartan in rats *in vivo*. The relative concentrations of glucuronide to parent compound at the 10 and 30 mg/kg doses decreased (Table 2.1.3.4 and 2.1.3.5), indicating a saturation of biotransformation at higher doses.

In conclusion, in the rat, after low oral doses, the glucuronidation by the gut is the most important biotransformation pathway. The apparent volume of distribution after i.v. and i.p.v. administrations decreased with the increase in dose, suggesting that the rat liver sequesters telmisartan in a dose-dependent manner.

TABLE 2.1.3.4

PHARMACOKINETIC PARAMETERS CALCULATED FROM RADIOACTIVITY, PARENT COMPOUND AND GLUCURONIDE BLOOD/PLASMA LEVELS IN THE *CAROTID ARTERY* AFTER I.D. ADMINISTRATION OF [^{14}C] TELMISARTAN TO MALE RATS

Parameter	Radioactivity Dose [mg/kg]			Parent compound Dose [mg/kg]			Glucuronide Dose [mg/kg]		
	1	10	30	1	10	30	1	10	30
C_{max} (C_{5min})	0.7751	26.53	66.04	0.1805	18.56	56.24	0.66	1.54	2.52
t_{max}	0.083	0.1716	0.2185	0.083	0.1847	0.2185	0.08	0.25	0.25
$t_{½}$	2.473	1.063	0.7792	2.362	1.068	0.8037	0.42	0.98	0.81
AUC_{0-5h}	0.4474	23.98	125.6	0.2788	18.64	109.6	0.14*	0.99*	2.31*
$AUC_{0-\infty}$	0.5414	24.56	127.8	0.3555	19.16	111.7	0.14	1.04	2.60
$AUC_{tf-\infty}$	16.81	2.256	1.722	20.3	2.61	1.97	0.69	0.95	4.50
MRT_{tot}	2.467	0.9871	1.523	3.057	1.084	1.582	0.36	0.66	1.09
CL_{tot}	30.80	6.787	3.912	46.87	8.702	4.475	117.90	160.09	192.05
V_z	6.593	0.6242	0.2639	9.585	0.8047	0.3113	4.31	13.54	13.47
V_{ss}	4.559	0.4020	0.3575				2.56	6.33	12.56

* AUC was only calculated from 0 to 2.5 h because of missing 5 h value.

TABLE 2.1.3.5

PHARMACOKINETIC PARAMETERS CALCULATED FROM RADIOACTIVITY, PARENT COMPOUND AND GLUCURONIDE BLOOD/PLASMA LEVELS IN THE *PORTAL VEIN* AFTER I.D. ADMINISTRATION OF [^{14}C] TELMISARTAN TO MALE RATS

Parameter	Radioactivity Dose [mg/kg]		Glucuronide Dose [mg/kg]	
	1	30	1$	30
C_{max} (C_{5min})	1.393	93.95	1.30	7.11
t_{max}	0.083	0.144	0.08	0.25
$t_{½}$	2.008	2.196	0.37	3.30
AUC_{0-5h}	1.085	227.9	0.26*	12.16*
$AUC_{0-\infty}$	1.327	285.4	0.28	31.34
$AUC_{tf-\infty}$	12.06	20.12	<0.01	26.89
MRT_{tot}	2.661	3.045	0.57	4.70
Cl_{tot}	12.56	1.752	60.29	15.95
V_z	2.183	0.3329	1.91	4.56
V_{ss}	2.006	0.3202	2.07	4.50

$: The last value for rats 1 and 2 was excluded from evaluation due to the fact that this value was unexpectedly high.

* AUC was only calculated from 0 to 2.5 h because of missing 5 h value.

2.1.4. Pharmacokinetics of Telmisartan-Glucuronide in Male Rats Following I.V. Administration During the Evaluation of the Pharmacodynamic Effect of Telmisartan-Glucuronide (Report #B768, Study #U97-2189)

This non GLP study was conducted by[ ] in January/February 1997. The objective of the study was to determine the pharmacokinetics and pharmacodynamics (the latter part is described in the Pharmacology section 1.1.2.1A(b)) of the 1-*O*-acylglucuronide metabolite of telmisartan in rats after i.v. bolus injection.

Telmisartan (batch #8230231) was initially suspended in PEG 200 followed by addition of 0.5 N NaOH and normal saline. The pH was adjusted to 5.2 with 0.5 N HCl. Telmisartan-glucuronide was dissolved in PEG 200 and diluted with normal saline. Rats were fed *ad libitum* and were not fasted. Two sets of experiments were conducted. (a) A group of 6 male rats weighing between 319 and 368 gm were administered single 50 mg/kg intravenous (bolus) doses of telmisartan. The injection volume was 2 ml/kg for 5 sec injected into the tail vein. Bile fractions were collected at 0-2, 2-4 and 4-6 h from all 6 animals in anesthetized condition. Telmisartan-glucuronide was isolated from these fractions as an amorphous white powder which, according to[ ] analysis, contained less than 0.1% of telmisartan. The identity of the product was confirmed by hydrolysis of telmisartan with ß-glucuronidase and by ^{1}H-NMR. (b) Two different doses of telmisartan-glucuronide, 1.34 and 4.02 mg/kg (molar equivalent to 1 and 3 mg/kg telmisartan, respectively), were administered i.v. (bolus) to anesthetized rats. Additional groups received i.v. doses of 0.3, 1 or 3 mg/kg telmisartan. Control animals received two different volumes (1 and 3 ml/kg) of vehicle (Table 2.1.4.1).

TABLEttt 2.1.4.1
COMPOSITION AND IDENTITY OF GROUPS

Group	Compound	N	Dose mg/kg	Sampling matrix	Investigation performed
1	Telmisartan	6	50	Bile	Isolation of telmisartan-glucuronide from bile
2	Telmisartan-glucuronide	6	1.34	Plasma	1. Pharmacodynamic activity 2. Conc. of T-G 3. Conc. of telmisartan 4. Pharmacokinetics of T-G
3	Telmisartan-glucuronide	6	4.02		
4	Telmisartan	3	0.3		1. Conc. of telmisartan 2. Conc. of glucuronide
5	Telmisartan	6	1		
6	Telmisartan	2	3		
7	Vehicle control	8	1 ml/kg		
8	Vehicle control	3	3 ml/kg		

Blood samples for the measurement of telmisartan-glucuronide and telmisartan were taken from the jugular vein of the anesthetized rats at: 0 (pre-dose), 0.025, 0.075, 0.2417 and 0.4917 hr after i.v. dosing. The possible pharmacodynamic effects of telmisartan-glucuronide were evaluated for 30 min after i.v. dosing. The results of the latter study are summarized in section 1.1.2.1A(b).

Results

After i.v. dosing of telmisartan-glucuronide, there was a rapid decline of plasma concentration of telmisartan-glucuronide (Table 2.1.4.1), suggesting that it was rapidly cleared from the plasma ($t_{1/2}$ 0.17 to 0.16 hr). The relative contribution of plasma concentrations later than 30 min to the overall AUC was negligible. Despite high concentrations of the telmisartan-glucuronide, there was no parent compound detectable in the plasma samples with the exception of 2/6 animals that were dosed at 1.32 mg telmisartan-glucuronide/kg and which had maximum telmisartan concentrations of approximately 27 ng/ml at 0 min sampling time. Thus, the study suggests that there is no clevage of the 1-*O*-acylglucuronide to the parent compound. The AUC values did not differ significantly between the two dosage groups (1.34 and 4.02 mg/kg) (Table 2.1.4.2), probably because of pronounced variability in the 1.34 mg/kg dosage group. The telmisartan-glucuronide AUC was approximately 5-fold lower than the telmisartan AUC determined in an earlier study (see Table 2.1.3.2 in section 2.1.3). Also, telmisartan-glucuronide exhibited a markedly higher clearance (125 ml/min/kg after 1.34 mg/kg) compared to the parent compound (15.6 ml/min after 1 mg/kg) (see Table 2.1.3.2). Because of this fast elimination, hydrolysis of the telmisartan-glucuronide to the parent compound is unlikely to occur to a relevant extent *in vivo*. The apparent volume of distribution at steady state (V_{ss}) for telmisartan-glucuronide was 0.39 l/kg (after dosing of 1.34 mg/kg), which is much lower than the V_{ss} for telmisartan (2.03 l/kg after i.v. dosing of 1 mg/kg (see Table 2.1.3.2).

Thus, it can be concluded that after intravenous administration of telmisartan, the systemic exposure to the telmisartan-glucuronide was very small compared to exposure to the parent compound. Since acyl glucuronides can react with plasma proteins forming covalent protein adducts, the short half-life and the low and short systemic exposure to telmisartan glucuronide is beneficial in reducing the risk of covalent binding of glucuronide to plasma proteins.

TABLE 2.1.4.1
PLASMA CONCENTRATION-TIME PROFILE OF TELMISARTAN-GLUCURONIDE (NG/ML) AFTER I.V. ADMINISTRATION OF TELMISARTAN-GLUCURONIDE TO MALE RATS

Time (hour)	N	1.34 mg/kg	N	4.02 mg/kg
	0	-	0	-
	6	3766	6	5761
	6	598.6	6	733.4
	6	44.42	6	52.05
	4	21.17	6	17.42

TABLE 2.1.4.2
PHARMACOKINETIC PARAMETERS OF TELMISARTAN-GLUCURONIDE AFTER I.V. ADMINISTRATION OF TELMISARTAN-GLUCURONIDE TO MALE RATS

Parameter	Unit	Dose, mg/kg	
		1.34	4.02
C_0	Ng/ml	9561	15500
C_{max}	Ng/ml	9556	15490
T_{max}	Hour	0.001904	0.002309
$t_{½}$	Hour	0.174	0.168
$AUC_{0-\infty}$	µg.h/ml	0.2643	0.3822
$AUC_{0-0.4917h}$	µg.h/ml	0.2221	0.3166
MRT_{tot}	Hour	0.05432	0.04467
MRT_{disp}	Hour	0.05243	0.04237
Cl_{tot}	Ml/min.kg	124.9	180.6
V_c	L/kg	0.2196	0.2698
V_{ss}	L/kg	0.3902	0.4630

Plasma concentrations of parent compound and its metabolically formed 1-*O*-acyl-glucuronide were determined for only one animal per dose level at doses of 0.3, 1 and 3 mg telmisartan/kg. Plasma concentrations increased in a dose-dependent manner. Plasma samples from rats dosed at 1 and 3 mg/kg, but not 0.3 mg/kg, showed the presence of metabolically formed telmisartan-glucuronide. (Table 2.1.4.3). Since the plasma concentrations of telmisartan in animals dosed with 1 mg telmisartan/kg were similar to the concentrations found at that dose in an earlier study (section 2.1.2), no pharmacokinetic analysis of telmisartan was undertaken in the present study.

TABLE 2.1.4.3
PLASMA CONCENTRATION-TIME PROFILE OF TELMISARTAN AND TELMISARTAN-GLUCURONIDE (T-G) AFTER I.V. ADMINISTRATION OF TELMISARTAN TO MALE RATS
Values are given as mean (ng/ml).

Time	0.3 mg/kg		1 mg/kg		3 mg/kg	
(h)	Telmistn	T-G	Telmistn	T-G	Telmistn	T-G
0.000	BLQ	NOP	BLQ	BLQ	BLQ	BLQ
0.0250	348.6	BLQ	1231	54.40	2990	54.43
0.0750	136.2	BLQ	436.0	20.96	1640	73.62
0.2417	90.07	BLQ	300.6	12.65	1197	62.22
0.4917	65.32	BLQ	198.6	12.95	979	56.81

N=1 per dosage
NOP: no peak found
BLQ: below lower limit of quantitation, (<5 ng/ml for telmisartan, <10 ng/ml for glucuronide)

2.1.5. Pharmacokinetics and Excretion Balance of [^{14}C]Telmisartan in Rabbits (Report #B337, Study #U95-2109)

This non GLP study was conducted by between April and August 1994. The objective of the study was to determine the basic pharmacokinetics and excretion of the administered radioactivity in female rabbits.

Three female rabbits weighing between 2.4 and 2.7 kg were used. The animals were fasted for 20 hr and were fed 2 hr after the administration of test substance. The dosage was 1 mg/kg [^{14}C]telmisartan (batch #Br 872/26) administered orally by gavage (volume 2 ml/kg). Test substance was dissolved in 1 N NaOH, diluted with 0.5% hydroxyethylcellulose and the pH was adjusted to 5 with 1 N HCl.

Levels of total radioactivity and parent compound were determined in blood/plasma collected from the central ear artery. Samples were collected at: 0, 0.5, 1, 2, 4, 6, 8, 24 and 48 hr after oral administration. Excretion of [^{14}C]telmisartan was determined by measuring radioactivity present in urine and feces. Urine samples were collected at 0-8, 8-24, 24-48 and 48-72 hr after dosing. Feces were collected as 24 hr fractions up to 96 hr.

Results

The absorption of the administered dose was slow (t_{max} = 7 hours). The terminal elimination half-life [$t_{½}$] of total radioactivity was approximately 15 hours and that of the parent compound was approximately 13 hours (Table 2.1.5.1). Thus, a moderate accumulation of the parent compound or of potential metabolites would be expected applying a once daily oral dose regimen in rabbits. The ratio of parent compound concentration to total radioactivity was approximately 0.5, indicating a relatively large portion of metabolites circulating in plasma.

TABLE 2.1.5.1
PHARMACOKINETIC PARAMETERS OF RADIOACTIVITY AND PARENT COMPOUND AFTER ORAL ADMINISTRATION OF 1 MG/KG [^{14}C] TELMISARTAN TO FEMALE RABBITS

Parameter	Radioactivity	Parent compound
C_{max} [ng-eqv/ml]	198	133
T_{max} [hour]	6.67	7.33
$t_{½}$ [hour]	14.6	13.2
AUC_{0-48} [ng-eqv·h/ml]	4570	2990
$AUC_{0-\infty}$ [ng-eqv·h/ml]	5360	3410
TCG [hour]	25.4	-
MRT_{tot} [hour]	-	24.0
Cl_{tot}/f [ml/min/kg]	3.25	5.07
$V_{z/f}$ [l/kg]	3.76	5.37

After oral administration the radioactivity was excreted predominantly (97.9% of the dose) by the fecal route; only 1.1% was detected in urine. The bulk of radioactivity (~ 87%) was excreted within the first 48 hours after dosing. Mean total excretion was essentially complete at 96 hr after oral administration (Table 2.1.5.2).

TABLE 2.1.5.2
CUMULATIVE EXCRETION OF TOTAL RADIOACTIVITY (% OF THE DOSE ADMINISTERED) AFTER SINGLE ORAL ADMINISTRATION OF 1 MG/KG [^{14}C]TELMISARTAN TO RABBITS (N=3/TIME POINT)

Time (hr)	Urine	Feces	Total excretion
	0.0597	-	-
	0.594	42.5	43.1
	0.958	86.6	87.6
	1.05	96.0	97.1
	1.07 + 1.08*	97.9	99.0

*:Cage wash

APPEARS THIS WAY
ON ORIGINAL

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

This non GLP study was conducted by

in March/April 1992.

Two male (11.8 and 13.1 kg) and two female (12.8 and 13.5 kg) beagle dogs each received single oral doses of 1 mg [^{14}C]telmisartan/kg (radioactive drug lot #KS 123/5, unlabelled drug lot #Ei 4465) by gavage (as a hydroxyethylcellulose suspension), and three weeks later, single i.v. bolus doses of 1 mg/kg in a cross-over design. The dogs were fasted for 12 hr prior to and during the first 2 hr after administration. For i.v. administration, test substance was dissolved in 0.5 M NaOH, diluted with normal saline and pH was adjusted with 0.5 M HCl. Total radioactivity was determined in blood, plasma (at various time points: 0 to 48 hr), urine (0-8, 8-24, 24-48, 48-72 and 72-96 hr) and feces (0-24, 24-48, 48-72 and 72-96 hr). Additionally, one male dog (12.4 kg) received a single i.v. dose of 1 mg/kg for studying excretion into bile. Bile was collected (from conscious animals) by inserting a cannula into the bile duct over the following intervals: 0-2, 2-4 and 4-6 hr. The bile fractions collected in this study were investigated for metabolite pattern and the results of that investigation are summarized in section 2.3.5.

Results

After oral administration of 1 mg/kg [^{14}C] telmisartan, peak blood levels of radioactivity were achieved in 1-2 hr in males, 4 hr in one female and 24 hr in the second female. In general, the data indicate a rapid absorption of telmisartan in this species. The extent of absorption, as calculated on the basis of AUC values derived from blood concentration-time profiles of radioactivity, was 19 and 22% in the 2 male dogs and 16 and 24% in the two female dogs. The concentrations of radioactivity and individual pharmacokinetic parameters derived from plasma are summarized in Table 2.1.6.1. The volume of distribution (mean of male and female dogs, 2.8 l/kg) was similar to the blood volume, suggesting that telmisartan is moderately distributed into tissue compartments. There was no difference in the ratios of the concentrations of total radioactivity in blood cells and plasma (0.73 to 1.92) determined at various time points after oral and i.v. administration of test compound, indicating equal distribution of the radioactivity into both compartments of blood. The absolute bioavailability, calculated on the basis of AUC values of parent compound, was 14 to 22% (Table 2.1.6.1). No significant sex-related differences were observed in this study. A comparison of the plasma-concentration time profiles of total radioactivity and parent compound, like in rats (see section 2.1.2), indicated that the parent compound is the predominant form of circulating telmisartan following both routes of administration.

TABLE 2.1.6.1
NON-COMPARTMENTAL PHARMACOKINETIC PARAMETERS OF PARENT COMPOUND IN PLASMA AFTER ORAL AND I.V. ADMINISTRATION OF 1 MG/KG [^{14}C] TELMISARTAN TO 2 MALE AND 2 FEMALE DOGS

Parameter	Radioactivity				Parent Compound			
	Intravenous		Oral		Intravenous		Oral	
	males	females	males	Males	males	females	Males	females
C_{max} [ng-eqv/ml]	1812	1729	50.1	14.1	1638	1586	35.1	12.2
	1570	1939	73.9	136.6	1452	1774	49.4	110.1
T_{max} [hour]			2.0	24			2	24
			1	2			2	2
$t_{½}$ [hour]			10.1	8.4	5.4	13.5	5.3	15.1
					12.5	19.9	4.1	5.7
$AUC_{0-\infty}$ [ng-eqv·h/ml]	2020	2120	337	357	1650	2030	234	330
	2110	2250	459	542	1990	2100	321	452
MRT_{tot}[hour]					6.5	4.9	5.5	33.1
					6.5	3.6	4.8	5.4
Cl_{tot}[ml/min/kg]					10.1	8.2		
					8.4	8.0		
V_{ss}[l /kg]					3.9	2.4		
					3.3	1.7		
F*			0.19	0.17			0.14	0.16
			0.22	0.24			0.16	0.22

*: absolute bioavailability factor

The radioactivity was rapidly eliminated from blood after i.v. administration; at 8 hr after administration, the blood concentrations of radioactivity ranged from 1.1 to 1.3% of maximum concentrations. At 8 hr after oral administration, the concentrations ranged from 10.1 to 31.5% of the maximum concentrations. The total recovery of the administered radioactivity after both routes of administration was complete at 96 hr post-dose. The fecal route was the dominant route of excretion of total radioactivity. The cumulative individual animal (n=2) fecal excretion was 86.1 and 94.4% for males and 97.8 and 98.7% for females after i.v. administration, and 95.4 and 98.7% for males and 91.7 and 97.7% for females after oral dosing. The 96 hr cumulative urinary excretion was in the range of only 0.06 to 0.7% of the dose after oral and i.v. administration in both sexes (Table 2.1.6.2).

Like the rat, the dog eliminated the radioactivity from blood into bile very fast (53.8% in 2 hr, 62.3% in 4 hr and 66.1% of the dose in 6 hr). It is possible that enterohepatic recirculation of parent compound occurred in some animals. A biphasic absorption with a second Cmax peak would indicate enterohepatic circulation of test compound or delayed absorption. However, this was not so clear in this study because of high inter-animal variability and small sample size.

TABLE 2.1.6.2.

CUMULATIVE EXCRETION OF TOTAL RADIOACTIVITY (% OF THE DOSE ADMINISTERED) AFTER SINGLE ORAL OR I.V. ADMINISTRATION OF 1 MG/KG [^{14}C]TELMISARTAN.

Values are mean from 2 male and 2 female dogs

Time (hr)	Oral			Intravenous		
	Urine	Feces	Total excretion	Urine	Feces	Total excretion
0-8	0.007	-	-	0.051	-	-
0-24	0.028	68.11	68.14	0.119	38.44	38.61
0-48	0.066	86.00	86.06	0.254	74.67	74.93
0-72	0.080	93.74	93.82	0.310	87.72	88.03
0-96	0.101	95.84	95.94	0.391	94.26	94.65

2.1.7. Pharmacokinetics of Telmisartan After Oral Administration to Fed and Fasted Dogs (Report #B53, Document #U92-0179)

This non GLP study was conducted by

between July 31 and August 5, 1991. The aim of the study was to determine the effect of feeding prior to administration on the plasma concentrations of telmisartan and thus to understand the absorption behavior of dogs towards telmisartan.

Six male (10 to 15 kg) beagle dogs each received single oral doses of 200 mg telmisartan (lot #8110110)/kg in a 0.5% hydroxyethylcellulose suspension by gavage either 30 min after feeding (fed state, n=3) or 7 hr prior to feeding (fasted state, n=3). In order to reduce the inter-animal variability, a cross-over regimen was performed after five days. Plasma concentrations of telmisartan were determined in blood samples collected at various time points: 0 to 48 hr post-dose.

Results

With the exception of one non-absorber in the fasted state, plasma concentrations were in the expected range in all animals. The "same dog in fed condition" changed to a poor absorber. In general, fed dogs had higher AUC values (+30%), higher Cmax values (+37%) and shorter Tmax (late phase, 15 vs. 24 hr) values than fasted dogs (Table 2.1.7.1). In addition, the biphasic plasma concentration-time profile characterized by two Cmax (and two Tmax) values in several animals was less pronounced in fed dogs than in fasted dogs. Food had no reducing effect on the variability of AUC and Cmax. Nevertheless, the sponsor recommends feeding the dogs 30 min prior to administration of telmisartan in order to obtain smaller variations in absorption.

TABLE 2.1.7.1
TELMISARTAN PHARMACOKINETIC PARAMETERS AFTER SINGLE 200 MG/KG ORAL ADMINSTRATION TO FED AND FASTED DOGS.
Results are given as Mean ± SD from 6 male dogs

Parameters	Fed dogs	Fasted dogs
AUC_{0-48h} [µg.h/ml]	323.3 ± 171.9	249.3 ± 195.7
C_{max} (1) [µg/ml]	14.3 ± 12.5	6.3 ± 10.3
t_{max} (1) [h]	7	1
C_{max} (2) [µg/ml]	22.7 ± 17.6	18.3 ± 10.6
t_{max} (2) [h]	15	24

2.1.8. Pharmacokinetic Profile of Telmisartan During One Week of Oral Administration to Dogs (Report #B67, Document #U92-0284)

This non GLP study was conducted by

(study dates not provided, report date April 30, 1992).

Chronically-instrumented (for measuring cardiovascular effects) male beagle dogs (10-15 kg) received oral doses of 10 and 160 mg telmisartan (lot #Ei4465)/kg in 0.5% hydroxyethylcellulose suspension by gavage (n=4/dose level) for 7 days. The dose formulation was administered 30 min after feeding. Plasma concentrations of telmisartan were determined in blood samples collected at intervals of 1 or 2 hours following administration on days 1, 2 and 7/8. Additional pre-dose plasma concentrations (trough levels) were measured on days 3, 4, 5 and 6.

Results

As noted in earlier two studies, the animals demonstrated a high inter-individual variability of plasma concentrations of telmisartan, particularly in the 160 mg/kg dose group. With a few exceptions (one low dose group dog and two high dose group dogs), highly delayed, and in several cases biphasic, plasma concentration profiles were observed. The mean AUC and Cmax values are summarized in table 2.1.8.1. No accumulation of the parent compound was observed in this study.

TABLE 2.1.8.1
PHARMACOKINETIC PARAMETERS FOR TELMISARTAN ON DAYS 1, 2 AND 7/8 IN DOGS ADMINISTERED ONCE DAILY ORAL DOSES OF 10 AND 160 MG/KG.
Results are given as Mean ± S.D

Parameters	10 mg/kg			160 mg/kg		
	day 1	day 2	day 7/8	day 1	day 2	day 7/8
AUC_{0-24h} [µg.h/ml]	2.32 ± 1.00	2.67 ± 0.45	2.70 ± 0.91	54.7 ± 42.3	165.3 ± 87.2	90.0 ± 55.1
AUC_{0-48h} [µg.h/ml]			3.80 ± 1.22			93.4 ± 55.6
C_{max} [µg/ml]	0.34 ± 0.33	0.34 ± 0.24	0.40 ± 0.36	15.6 ± 11.3	15.8 ± 6.46	10.0 ± 6.17
t_{max} [h]	2.25 ± 0.50	3.00 ± 2.16	2.25 ± 0.50	3.0 ± 0.82	8.5 ± 7.7	6.75 ± 4.99

2.1.9. Plasma Levels of Telmisartan After Single Dose Administration to Animals & Humans

Pharmacokinetic and toxicokinetic profiles of telmisartan following single dose administration in various species are discussed individually under ADME and toxicology studies. The plasma concentration profile documented in each of these studies is summarized below in a tabular form.

Species	Route	Dose mg/kg/d	Sex	C_{max} µg/ml	T_{max} h	$T_{1/2}$ h	$AUC_{0-\infty}$ - µg.h/ml	V_{ss} l/kg	Cl, ml/ min/kg	F	Ref. Sec #
Mouse	Gavage[1]	1	M	0.183	2	10.1	1.787	-	-	0.82	2.1.1
			F	0.238	2	8.4	2.019	-	-	0.62	
	IV, bolus[1]	1	M	0.552	0.08[2]	9.5	2.180	5.9	10	-	
			F	0.581	0.08[2]	8.5	3.272	3.3	6.4	-	
Rat	Gavage[3]	1	M	0.053	2	7.0	0.732		24.0	0.67	2.1.2
	IV, bolus[3]	1	M	0.577		6.52	1.144	5.28	14.6		
	i.d.[1,4]	1	M	0.775	0.083	2.47	0.54				2.1.3
		10		26.53	0.172	1.063	24.56				
		30		66.04	0.219	0.78	127.8				
	IV, bolus[1]	1	M	0.85	0.088	1.7	1.231	1.68	13.54		
		10		34.27	0.083	1.02	33.22	0.31	5.02		
		30		123.0	0.083	0.81	166.00	0.23	3.01		
	IPV, bolus[1]	1	M	1.195	0.083	2.074	1.397	1.561	11.93		
		10		36.85	0.083	1.037	35.42	0.303	4.72		
		30		119.4	0.083	1.131	191.0	0.262	2.62		
Rabbit	Gavage	1	F	0.198	6.67	14.6	5.36	-	3.25	-	2.1.5
Dog	Gavage[5]	1	M	0.0423	2	4.7	0.278			0.15	2.1.7
			F	0.0612	2	10.4	0.391			0.19	
	IV, bolus[5]	1	M	1.545		8.95	1.820	3.6	9.25		
			F	1.680		16.7	2.065	2.05	8.10		
	Gavage[6]	200	M	14, 23[8]	7, 15[8]		323.3[9]				2.1.6
	Gavage[7]	200	M	6, 18[8]	1, 24[8]		249.3[9]				
Human[10]	Soln./oral	40 mg[11]	M	0.447	1.0	13.8	0.491		19.4	0.43	study #502.110
	IV, infusion	40 mg	M	1.196		19.5	1.132		8.4		
	Tablet	40 mg[12]	M	0.0210	1.5	19.2	0.288				study #502.113
		40 mg[13]	M	0.0163	2.5		0.280				
	Tablet	80 mg	M	0.209	0.75[14]	13.1	1.119[15]				study #502.109
	Tablet	160 mg	M	1.240	0.5	18.9	2.180			0.574	study #502.112
	IV, infusion	160 mg	M	3.290		18.3	3.590				

(see next page for footnotes)

The values are for total radioactivity in studies where radiolabeled telmisartan was administered
F: fraction of drug absorbed, $AUC_{oral}/AUC_{i.v.}$
1: fasted for 16 hr before administration; 2: first time point; 3: fasted for 20 hr before administration;
4: total radioactivity determined in blood collected from carotid artery; 5: fasted for 12 hr prior to administration;
6: drug administered 30 min after feeding; 7: drug administered 7 hr prior to feeding;
8: biphasic plasma concentration-time profile; 9: AUC_{0-48h}; 10: healthy volunteers; 11: 40 mg total dose is equivalent to 0.8 mg/kg; 12: fasted; 13: fed; 14: median; 15: AUC_{0-24h} is 0.867 µg.h/ml

APPEARS THIS WAY
ON ORIGINAL

2.1.10. Plasma Levels of Telmisartan After Repeated Dose Administration to Animals & Humans

Pharmacokinetic and toxicokinetic profiles of telmisartan following repeated dose administration in mice, rats, rabbits and dogs are discussed individually under ADME and toxicology studies. The plasma concentration profile documented in each of these studies is summarized below in a tabular form.

Animal species	Studies	Inter-val	Admin	Dose mg/kg/d	C_{max} µg/ml		AUC_{0-24} µg.h/ml		Ref. Sec #
					M	F	M	F	
Mouse	Oral 13-wk	wk 14	Drug-diet mix	30			10.7[a]	12.84[a]	3.4.1
				100			38.9	43.38	
				300			70.58	168.99	
				1000			284.6	426.03	
	Oral 104-wk	wk 99-101	Drug-diet mix	10			3.87[a]	6.39[a]	3.4.2
				100			6.67	57.39	
				1000			445.7	759.10	
Rat	Oral 4-wk	day 14	gavage	10	0.4	0.5	5.5	6.8	3.2.1.
				50	4.2	2.4	25.9	20.7	
				100	37.3	53.5	246.4	158.9	
				200	74.7	49.0	750.8	275.1	
		day 28	gavage	10	0.3	0.4	3.7	5.4	
				50	2.5	3.0	22.2	35.4	
				100	53.6	42.5	271.5	173.9	
				200	78.8	50.6	858.9	411.9	
	i.v. 4-wk	day 28	bolus, in 0.5 min	0.1	0.07	0.07	0.15[b]	0.15[b]	3.2.3
				2.0	1.89	1.93	3.07[b]	3.22[b]	
				20.0	91.10	89.90	123.30[b]	93.30[b]	
	Oral 13-wk	wk 13	gavage	2	0.08	0.10	1.09	1.35	3.2.4
				4	0.22	0.29	2.76	2.09	
				8	0.42	0.55	5.04	5.22	
				500	81.10	119.00	796.00	1410.00	
	Oral 26-wk	wk 26	gavage	0.1	0.0062	0.0106	0.105	0.095	3.2.5
				1	0.0595	0.0802	0.706	0.698	
				4	3.3200	3.5900	30.900	38.600	
				50	21.8000	29.5000	123.000	124.000	
				500	76.8000	173.0000	1030.000	1570.000	
	Oral 104-wk	mo 3	Drug-diet mix	3			2.17	2.33	3.4.4
				15			14.01	13.39	
				100			162.12	137.80	
		mo 6		3			2.50	2.44	
				15			13.70	15.34	
				100			156.05	221.92	
		mo 12		3			3.28	3.69	
				15			22.80	22.75	
				100			176.00	240.02	
		mo 24		3			3.83	5.53	
				15			24.52	18.04	
				100			428.18	276.43	

Animal species	Studies	Inter-val	Admin	Dose mg/kg/d	C_{max} µg/ml		AUC_{0-24} µg.h/ml		Ref. Sec #
					M	F	M	F	
Rabbit	Oral GD 6-18	GD 13	gavage	5		1.42		8.57[b]	3.5.4
				15		6.39		37.51[b]	
				30		16.78		90.78[b]	
Dog	Oral 1-wk	day 7/8	gavage	10	0.40		2.70		2.1.7
				160	10.0		90.00		
	Oral 4-wk	day 25	gavage	10	0.4	0.5	7.0	7.0	3.2.6
				40	1.7	5.2	21.0	57.2	
				160	12.8	15.8	170.3	122.7	
	I.V. 4-wk	day 24	bolus, 3 sec to 5 min	0.5	2.81	7.40	1.49	2.11	3.2.7
				5.0	18.62	51.92	16.43	21.81	
				50.0	214.13	312.89	282.05	338.73	
	Oral 13-wk	day 91	gavage	5	0.20	0.28	3.2	3.1	3.2.8
				10	0.28	0.85	3.9	9.2	
				20	2.00	1.20	20.4	14.4	
				50	5.10	4.00	51.1	47.0	
	Oral 52-wk	day 193	gavage	5	0.158	0.206	2.082	2.593	3.2.9
				50	1.737	3.009	23.667	39.421	
				500	21.019	35.593	240.767	387.343	
		day 319		5	0.120	0.170	1.866	2.359	
				50	1.777	1.730	21.307	26.461	
				500	11.562	31.047	134.396	352.200	
		day 361		5	0.119	0.228	1.947	3.454	
				50	1.804	4.336	24.777	47.399	
				500	17.080	23.340	177.545	250.918	
Human	7-day[c]	SS	tablet	320 mg[d]	4.641[ss, f]	-	6.124[ss, f]		Study #502.115
	7-day[c, g]	SS	tablet	120 mg[d]	0.329[ss]	1.060[ss]	2.040[ss]	2.380[ss]	Study #502.124
	7-day[c]	SS	tablet	120 mg[d]	0.451[ss]	1.290[ss]	1.050[ss]	2.530[ss]	Study #502.128
	7-day[e]	SS	solution	120 mg	2.017[ss, f]		5.743[ss, f]		Study #502.201
				160 mg	2.871[ss, f]		5.357[ss, f]		
	28-day[e]	SS	capsule	120 mg	1.635[ss, f]		5.657[ss, f]		Study #502.202

a: estimated value, obtained by multiplying the means of two time points, 8 and 16 hr by 24.
b: AUC_{0-7h} ; c: healthy volunteers ; d: q.d.; e: hypertensive patients; f: average of male and female data.
g: elderly subjects to study gender differences; ss: steady state;

2.2. Distribution (including Plasma Protein Binding)

A study investigating the tissue distribution of telmisartan in rats is given under section 2.1.2 as a part of pharmacokinetics (absorption). Placental transfer of telmisartan after oral administration in rats on days 12 and 18 of pregnancy is summarized in section 3.5.5.

2.2.1. Protein Binding of [^{14}C]Telmisartan in Rat, Mouse, Dog and Human Plasma

Rat, Dog and Human Plasma: Report #B122; Document #U93-0386. Telmisartan: lot #ks 123/5. Study period: March-April 1992.
Mouse and Human Plasma: Report #B155; Document #U95-2063. Telmisartan: lot #Br 872/26. Study period: July 1993 (human plasma) and January 1995 (mouse plasma).

This non GLP study was conducted by The study investigated the extent of binding of [^{14}C]telmisartan *in vitro* to rat, dog and human plasma proteins at pharmacologic and toxicologic concentrations. Protein binding was determined by ultrafiltration and ultracentrifugation methods.

Individual plasma samples were prepared from pooled blood samples obtained from fifty male and female mice (not fasted), five male albino rats (fasted for 20 hr prior to blood collection), two female dogs (strain not reported) (fasted for 20 hr), and two (one for each study) healthy male volunteers (2 hr after food). Protein binding was investigated in the concentration range 100-5000 ng/ml [^{14}]telmisartan (lot #ks 123/5) in human plasma, 100 and 500 ng/ml in dog plasma, 100-10,000 ng/ml in rat plasma and 300-30,000 ng/ml in mouse plasma. The plasma samples containing added [^{14}C]telmisartan (solution prepared in a mixture of absolute ethanol and 1 N NaOH, diluted to desired volume and concentration with physiological saline and pH adjusted to the range of 7-8) were incubated for 2 hr at 37°C. Aliquots were removed before and after the incubation and their radioactivity was counted. After the incubation, ultrafiltration (performed for human, dog and rat plasma) or ultracentrifugation (human and dog plasma only) was performed.

Results

The mean extent of binding to plasma proteins appeared to be independent of the concentration and the method of determination. The binding percentage of the drug remained fairly high and constant in all species examined (98.7-99.6%) (Table 2.2.1.1). The free fraction of telmisartan in the dog plasma (1.3%) was three times higher than the free fraction of telmisartan in plasma of humans and rats (0.4%). Because of the high extent of plasma protein binding observed, the pharmacokinetics of telmisartan could potentially be affected by the presence of other protein-bound drugs. Further, higher binding to protein results in slower metabolism of the parent compound in both animals and humans.

TABLE 2.2.1.1

MEAN VALUES (±SD) OF [^{14}C] TELMISARTAN BINDING TO PLASMA PROTEIN EXPRESSED IN PERCENT OF ADDED RADIOACTIVITY OBTAINED BY ULTRAFILTRATION (UF) OR ULTRACENTRIFUGATION (UC) IN VARIOUS SPECIES. (U93-0386, U95-2063).

species	number of animals/ sex	number of samples determined	concentration [µg/ml]	percent of drug bound	method of determination
mouse	50 / M	4	30	98.99 ± 0.03	UF
		4	0.3	99.26 ± 0.12	UF
	50 / F	4	30	99.40 ± 0.02	UF
		4	0.3	99.61 ± 0.04	UF
rat	5 / M	2	10	99.23	UF
		2	1	99.37	UF
		3	0.5	99.58 ± 0.02	UF
		3	0.1	99.56 ± 0.11	UF
dog	2 / F	5	0.5	98.73 ± 0.08	UF/UC
		5	0.1	98.70 ± 0.15	UF/UC
human	1 / M	7	5	99.60 ± 0.06	UF/UC
		7	0.5	99.65 ± 0.04	UF/UC
		6	0.5	99.57 ± 0.01	UF/UC
		7	0.1	99.58 ± 0.08	UF/UC

2.3. Metabolism

2.3.1. Metabolism of Telmisartan Following a Single Oral or Intravenous Administration of [^{14}C]Telmisartan to Mice (Report #B729, Study #U97-2190)

This non GLP study was conducted by

between April and December 1996.

The dosage was 10 mg/kg [^{14}C]telmisartan (lot #Ag 66/2) administered orally (n=10/sex) by gavage (10 ml/kg) and i.v. (13 male/17 female) (5 ml/kg) by bolus injection (duration 5 sec) into the tail vein . The weights of the mice (strain used in this study were in the range of 27-51 gm. The animals were fasted for 16 hr and were fed 1 hr after the administration of test substance. Test substance was dissolved in 0.5 N NaOH. The preparation was diluted with normal saline and the pH was adjusted to 8-9 with 0.5 N HCl. The concentration was 1 mg/ml for oral and 2 mg/ml for i.v. administration.

Blood samples were collected from individual mice at time points 2 or 6 h after oral drug administration only. Bile was collected from i.v. dosed mice only. Biliary excretion of test substance or its metabolite was determined by inserting a cannula into the bile duct and the bile collected in fractions at various intervals up to 6 hr after administration.

Results

Most of the orally administered radioactivity was represented by the parent compound, whereas only a small fraction (6 to 13% of total radioactivity) was attributable to metabolites. 1-*O*-acylglucuronide was the main metabolite. Minor amounts of radioactivity attributable to rearrangement products of the 1-*O*-acylglucuronide (formed by non-enzymatic acyl migration) were also observed.

Following intravenous administration, the main metabolite detected in bile was the 1-*O*-acylglucuronide of [^{14}C]telmisartan (50-80% of total radioactivity). In addition to rearrangement products of the 1-*O*-acylglucuronide (4-16%) formed by non-enzymatic acyl migration, and the parent compound (2-32%), another metabolite (5-11% of total administered radioactivity) was observed in the bile sample. This product (Mx) was identified as a glycoside of the parent compound (telmisartan conjugated to a hexose sugar). The latter metabolite has not been observed in any other species studied, including man.