CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 20-838

MEDICAL REVIEW(S)

Addendum to Secondary NDA Medical Review

NDA #: 20-838 **Sponsor:** Astra Merck
Drug Name: Candesartan Cilexetil (ATACARD™) **Date Completed:** 3/30/98
Medical Reviewer: Charles J. Ganley, M.D.

There were several issues left unresolved in the secondary medical review that require further clarification.

Chemistry

Acceptable EERs have been obtained for Astra Hassle AB, Astra Pharmaceutical Products, Takeda Chemical Industries. For Yoshitomi Pharmaceutical, Inc., the inspection has been completed but the EER has not been issued.

Efficacy

The following table outlines the trough/peak ratios from four clinical trial. Peak blood pressure was obtained 6 ± 2.5 hours after dosing. All values are $\geq .7$. This is either the most amazing anti-hypertensive agent or the methodology of calculating the trough/peak is flawed. The reverse dose response observed in study AM113 raises questions regarding the timing of the peak measurements.

Trough/Peak Ratio for DBP.

Dose	Protocol AM113	Protocol AM116	Protocol AM119	SH-AHM-0001
2 mg	2.0			
4 mg	2.0			
8 mg	1.5			1.1
16 mg	.98	.7	.8	.88
16 BID		.8	.7	
32 mg	1.2			

It should be noted that Dr. Fiddes[1] participated in studies 113 and 119. If data from his center is excluded from the analysis for those studies, there is still a significant benefit observed with candesartan compared to placebo.

Safety

Dr. U's review noted that two patients experienced hepatitis. After reviewing the case report forms, Dr. U determined that Patient 015/0088 (study EC040) discontinued due to chest pain and not hepatitis. Liver function tests were mildly elevated. Patient 0028/0192 (study EC040) had elevated SGPT and bilirubin (95 IU/L and 1.9 mg/dl respectively). On subsequent testing, the patient had positive IgM and IgG for hepatitis A. (see Dr. U review dated 3/27/98)

Upon futher questioning of the sponsor, Dr. U has determined that there are two cases of angioedema in patients receiving candesartan. In one case, seafood may have contributed to the angioedema.

Charles J. Ganley, M.D.

cc: orig. to NDA
HFD-110 Division File
HFD-110 / Project Manager / C. Ganley /S. Fredd / Khin U / A. Proakis
HFD- 710 / K. Mahjoob
HFD- 810 / J. Piechocki
HFD-860 / A. El-tahtawy / A. Parekh

[1] currently, Dr. Fiddes is under investigation for misrepresentation of data

K. Borgovanni

APR 9 1998

Statistical Review and Evaluation

Attachment to the Secondary Medical Review of Candesartan

Additional Analysis on Study AM-116 Data

DATE:

NDA #: 20-838

APPLICANT: Astra Merck Inc.

NAME OF DRUG: ATCAND (Candesartan)

DOCUMENTS REVIEWED: Vol. 8-47 (Vol. 108 of 498)

Introduction:

This report contains the analyses requested by Dr. Charles Ganley, the Medical Team Leader, from the Division of Cardio-Renal Drug Products (HFD-110), in association with his secondary review of Candesartan. This will be an attachment to Dr. Ganley's review and therefore, the purpose is only to present the results with no interpretation and drawing a conclusion.

Analysis

In Study AM-116, patients were randomized to placebo or candesartan for a double blind treatment period of 8 weeks. During the first 4 weeks patients were receiving placebo or candesartan 8 mg (**C_8mg_QD**) once-a-day. Thereafter, at the beginning of Week 5 (**Visit 8**), the dose of patients in the candesartan group was titrated to either candesartan 8 mg BID (**C_8mg_BID**) or candesartan 16 mg QD(**C_16mg_QD**). Placebo patients continued to receive the placebo.

Dr. Ganley wanted to find out, if after 4 weeks of C_8mg_QD therapy, there was further reduction in patients blood pressure as a result of the candesartan dose escalation. This exploration should be conducted, separately, by "**Responders**" and "**Non-Responders**" to the therapy at Week 4, as defined below:

Responder: SiDBP at week 4 < 90 mmHg or Reduction in SiDBP for Baseline to Week 4 > 10 mmHg .

Considering this objective, the following analyses were conducted:

Statistical Reviewer: Kooros Mahjoob

Step 1: This is a graphical exploration of the profiles of the sitting diastolic blood pressures (**SiDBP**) from the baseline (**Visit 5**) to Week 8 (**Visit 10**) to visualize the patients' response to the therapy in the entire course of the active treatment. The results are represented bu **Figures I** and **II**.

Figure I: Profiles of SiDBP for the Non-Responders to Therapy at Week Four

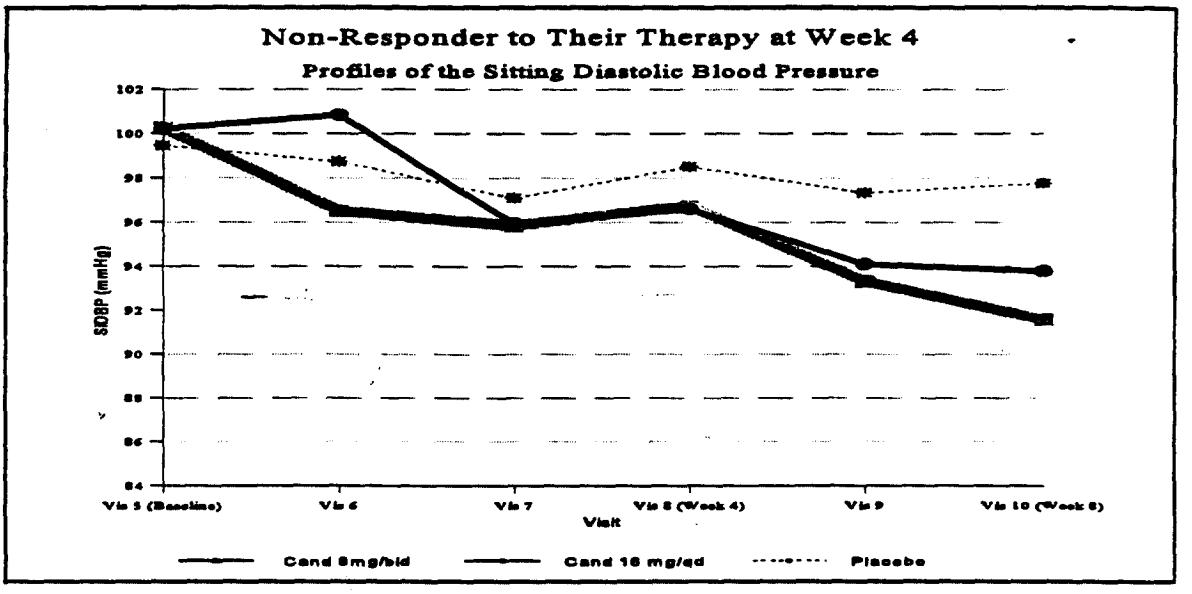
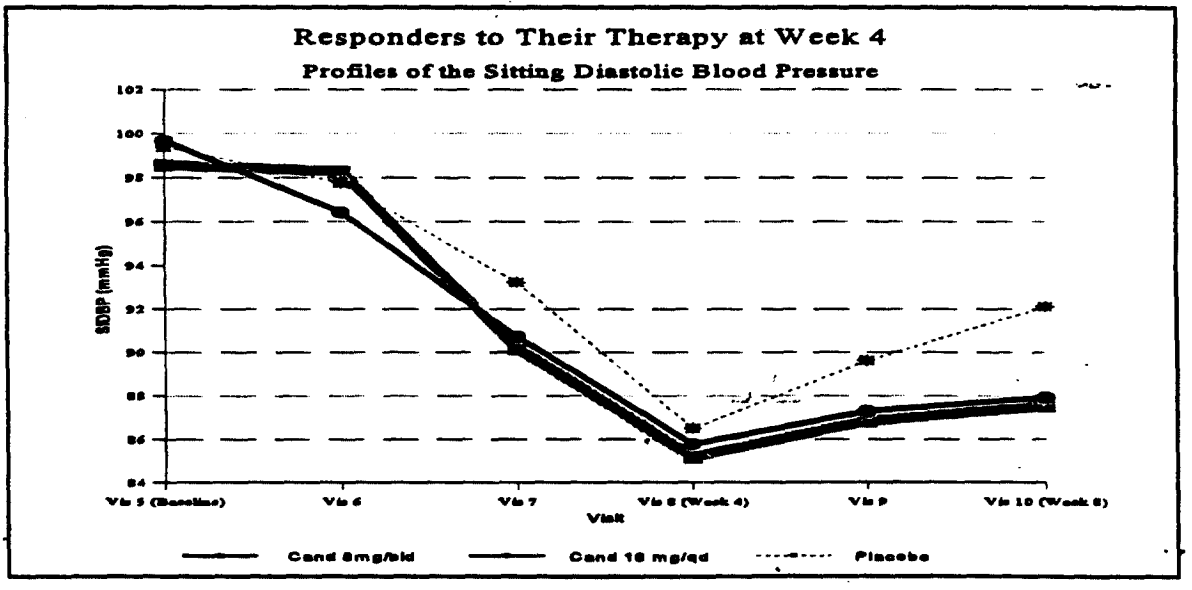


Figure II: Profiles of SiDBP for the Responders to Therapy at Week Four



Statistical Reviewer: Kooros Mahjoob

As can be seen from these figures, only the non-responders have demonstrated a further benefit as a result of dose titration.

Step II. This step is the numerical presentation of the results presented via Figures I and II and also to conduct a statistical test to see if the mean reductions in SiDBP observed for the non-responder's and the mean increase in SiDBP observed for the responder's are statistically significant. **Table I** presents comparison between Week 8 and Week 4 with respect to the SiDBP. The magnitudes in Table I are:

$$\mathbf{SiDBP\_8\_4 = SiDBP\_8 - SiDBP\_4}$$

The conducted test is:

$$\mathbf{Ho: Mean\ Change\ in\ SiDBP\_8\_4 = 0 \quad vs. \quad Ha: Mean\ Change\ in\ SiDBP\_8\_4 \neq 0}$$

Table I: Mean and Standard Deviation for Change from Week 4 to Week 8 and the P-Values

		Sitting Diastolic Blood Pressure			
		n	Mean	SD	P-Value
Non-Responders	Placebo	63	-0.75	8.63	0.4952
	C_8mg_ BID	44	-5.14	6.07	0.0001
	C_16mg_QD	38	-3.19	7.45	0.0120
Responders	Placebo	21	4.08	7.26	0.0180*
	C_8mg_ BID	45	2.20	7.11	0.0439*
	C_16mg_QD	46	1.72	6.30	0.0700

*: Although, statistically significant, the results have gone in opposite direction.

The results show that, for the non-responders at Week 4, further reduction in SiDBP at Week 8 is statistically significant. For the responders at Week 4, the changes in SiDBP are in unfavorable direction.

Kooros Mahjoob, Ph.D.
Mathematical Statistician

This review consists of 4 pages which includes two figures and one table.

Concur: Dr. Chi 4/9/98

CC:

Arch. NDA 20-838, ATCAND (Candesartan).

HFD-110

HFD-110/Dr. Ganley
HFD-110/Mr. Bongiovanni
HFD-344/Dr. Barton
HFD-710/Dr. Chi
HFD-710/Dr. Mahjoob
HFD-710/Chron.

K. Mahjoob: 4-5301:Biometrics 1/Team 1:km.

APPEARS THIS WAY
ON ORIGINAL

K. Borgcramm
MAR 24 1998

Secondary NDA Medical Review

NDA #: 20-838
Drug Name: Candesartan Cilexetil (ATACARD™)
Medical Reviewer: Charles J. Ganley, M.D.

Sponsor: Astra Merck
Date Completed: 3/20/98

Primary Reviewers
Chemistry: Joseph Piechocki, Ph.D.
Environmental Assessment: Florian Zielinski, Ph.D.
Pharmacology: Anthony Proakis, Ph.D.
Medical Efficacy: Stephen Fredd, M.D.
Medical Safety: Khin U, M.D.
Statistics: Kooros Mahjoob, Ph.D.

Chemistry

The sponsor plans to market a 4 mg, 8 mg, 16 mg and 32 mg tablet. This differs from the original submission in that the 32 mg tablet was not included. There are several outstanding deficiencies that are noted in review #3 from Dr. Piechocki (2/3/98). The deficiencies include problems associated with:

A request for methods validation will not be forwarded until the deficiencies listed above are resolved.

It appears that acceptable EERs have not been obtained[1] for Astra Hassle AB, Astra Pharmaceutical Products, Takeda Chemical Industries

Pharmacology

Candesartan cilexetil was studied in numerous models to detect effects on the Cardiovascular System, Gastrointestinal System and CNS and Somatic Nervous Systems.[2] Outside of the cardiovascular system, there is very little or no effect. Several renin sensitive models of hypertension in the rat and dog illustrated the blood pressure lowering effect of candesartan.

In rats and mice, single high intravenous or intraperitoneal doses of candesartan (≥ 910 mg/kg), MII (the inactive metabolite of candesartan; ≥ 1000 mg/kg) and cyclohexanediol (the cilexetil hydrolyzed product; ≥ 1240 mg/kg) caused ataxia, respiratory depression, decreased motor activity and death.

Repeat oral gavage for 6 months in rats caused erosions in the stomach, renal tubular hypertrophy, renal tubular basophilia, decreases in erythroid parameters and increases in blood urea nitrogen. No severe toxicity was seen. Repeat oral dosing by dietary administration for up to 2 years showed marginal reduction in erythroid parameters. The gastric erosions observed with gavage did not occur with dietary administration of candesartan.

The carcinogenicity data was reviewed by the FDA Executive Carcinogenicity Committee on 2/10/98. The committee concluded that the rat and mouse studies were acceptable and there was no carcinogenic potential observed.

Developmental toxicity studies were performed in the rat, mouse and rabbit. No fetal abnormalities were observed in any of the species. Maternal toxicity was observed in the rabbit (↓ body weight and death). In a peri- and post-natal toxicity study in rats, there was slight maternal toxicity (slight ↓ in food consumption and slight ↓ in body weight). Neonatal survival was reduced and the incidence of hydronephrosis increased with doses > 10 mg/kg.

There was no mutagenic or clastogenic potential exhibited.

Clinical Pharmacology

Candesartan cilexetil is a racemic mixture, contains one chiral center and is a non-active prodrug. Candesartan cilexetil levels are measurable in plasma but less so after oral dosing compared to intravenous

[1] they have been assigned but await inspections
[2] see p. 11 - 13 of Dr. Proakis review

administration.[3] It is rapidly and completely hydrolyzed to candesartan. The absolute bioavailability of candesartan is approximately 14%. Because none of the studies directly compared the tablet with intravenous administration, the absolute bioavailability was derived from the results of study SH-AHC-0005 (tablet vs. solution) and study SH-AHC-0001 (oral solution vs. intravenous formulation).[4] Candesartan is an AII receptor antagonist.[5] The angiotensin II antagonist activity was demonstrated in humans by blocking the AII induced blood pressure elevation (study EC008), by increasing renin and angiotensin II levels and by showing no change in ACE activity. Aldosterone decreased with increasing candesartan cilexetil dose in two studies (EC021, EC037).

The majority of phase III trials were performed using a formulation manufactured by Takeda Chemical Industries. Astra Merck will manufacture the market tablet. The Astra Merck tablet is bioequivalent to the Takeda formulation (study SH-AHC-0004).

Unlike candesartan cilexetil, candesartan is achiral. It is predominately excreted unchanged in the urine but does undergo some hepatic metabolism (probably by p-450 CYP2C) to an inactive metabolite, MII (CV15959).[6] Table CP.1 lists the amount of radioactivity collected in the feces and urine after oral solution or intravenous administration. The percentage of radioactivity collected in the urine with i.v. dosing is greater than that observed with oral solution dosing. This reflects the incomplete absorption of candesartan from the gastrointestinal tract. The amount of unchanged drug found in the urine was 52% and 26% for the i.v and oral solution respectively.

Table CP.1. Percent Radioactivity collected in the feces and urine

Dose Administration	Urine	Feces
Intravenous	59%	36%
Oral Solution	33%	68%

Numerous studies were performed to assess the pharmacokinetics of candesartan. C_{max} and AUC increase in a dose proportional manner (study TCV-116). The elimination half-life ($t_{1/2}$) is approximately 9 hours.[7] The pharmacokinetic parameters are similar in males and females. In subjects ≥ 65 years of age, both C_{max} and AUC were greater by 80% and 50% respectively compared to younger adults (18 - 40 years) but there was no difference in $t_{1/2}$ between age groups. Patients with mild (Cr. Cl. > 60 ml/min/1.73 m^2 ; N = 9) and severe (Cr. Cl. 15 - 30 ml/min/1.73 m^2 ; N = 7) renal dysfunction were evaluated for pharmacokinetic parameters. There was a progressive increase in AUC, C_{max} and $t_{1/2}$ with decreasing renal function.[8] Food did not change the AUC but did increase the C_{max} and decrease the T_{max} (by 1 hour).

Drug interaction studies were performed with HCTZ, nifedipine, digoxin, warfarin[9], glyburide and oral contraceptives (ethinyl estradiol + levonorgestrol). There were no changes in the pharmacokinetics of candesartan or the comparator when administered concomitantly with nifedipine, digoxin, glyburide and oral contraceptives. When candesartan was given with HCTZ, the AUC of candesartan increased by 18% whereas the AUC of HCTZ decreased by 14%. It should also be noted that the AUC of the MII metabolite also increased by 21% with concomitant HCTZ. This interaction may reflect an effect of HCTZ on the renal excretion of candesartan and MII.

A pharmacokinetic/pharmacodynamic study with concomitant warfarin was performed (study TCV-116/EC032). Twelve subjects were started on warfarin until a stable INR was achieved. Candesartan 16 mg was administered concomitantly for 9 days. After 9 days, candesartan was stopped and warfarin continued for an addition 6 days. There was no significant changes in INR. There was a 6% decrease in warfarin concentration.[10]

Candesartan is 99.5% protein bound. In patients with severe (Cr. Cl. 15 - 30 ml/min/1.73 m^2) renal dysfunction, protein binding was 99.2%. Although this .3% difference appears trivial, it represents a 60% increase in free fraction.

The Biopharm reviewer's recommendations for dissolution testing are outlined in appendix IV of the Biopharm review.

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[3] As an oral solution, candesartan cilexetil C_{max} were approximately 4% of the candesartan C_{max}. No candesartan cilexetil was detected with oral tablets (.5 - 16 mg).

[4] The absolute bioavailability of the solution compared to the i.v. formulation is .42. The relative bioavailability of the tablet compared to the solution is .34. Absolute bioavailability of tablet = (tablet/solution) x (solution/i.v.) = .34 x .42 = .14.

[5] the receptor affinity for AT_1/AT_2 is 10,000 in the Biopharm review and 500 in pharmacology review

[6] MII was formed in vitro with CYP2C isoenzymes. The cilexetil moiety is cleaved to yield cyclohexanediol.

[7] elimination $t_{1/2}$ of MII metabolite was approximately 10.4 hours (study AAC-0001)

[8] p. 11, table 2 of Biopharm Review

[9] warfarin is metabolized by CYP 2C9 and is extensively protein bound

[10] It is not clear whether this was total or free warfarin.

Exposure

The original NDA database includes information on 5388 subjects. The majority of subjects (N = 4922) were enrolled in phase II/III trials. Of these, 2831 received candesartan, 673 received candesartan + HCTZ and 89 received candesartan + amlodipine. The majority of subjects had less than 12 weeks of exposure to candesartan. Long term exposures of ≥ 24 weeks was available in 452 subjects. The placebo-controlled trials in hypertensives enrolled 1946 candesartan and 758 placebo patients [page 9 med/stat. review]. The majority of exposure occurred with ≤ 16 mg of candesartan. There was limited exposure with 32 or 64 mg.

Efficacy

The original NDA included the results from 14 placebo-controlled trials in hypertensive patients. The double-blind treatment periods in the controlled studies ranged from 4 weeks to 12 weeks. The daily dose of candesartan studied in the trials ranged from 2 mg to 64 mg. The majority of the exposure is with 16 mg or less per day. Several studies included an active control (enalapril, losartan, or amlodipine) in addition to a placebo control. The sponsor had incorporated a variety of designs into the clinical program as illustrated in the Table EF.1.

Table EF.1. Types of Studies Performed in Hypertensive Patients. [All Studies are Double-Blind unless otherwise indicated. Does not include single dose or single center trials.]

Type of Study	Protocol Number
Placebo Controlled	AM113, EC047, EC403, EC009
Placebo and Active Controlled	EC018, EC033, AH-AHM-0006, EC011
Placebo Controlled, Optional Titration	AH-AHM-0002, EC018, AH-AHM-0004
Placebo Controlled, Forced Titration	AM119, AM116
Peak	AM113, AM116, EC047,
Twice-a-Day Dosing	AM116
Open Label	AM116 extension, EC012, EC015, EC040, EC403 extension, AM117 extension
Placebo-controlled , Non-responder to HCTZ	EC 016
With HCTZ	AM117
Placebo Controlled, Factorial Trial with HCTZ	EC403
Blinded Controlled Withdrawal	EC012, EC040
ABPM	AM113 ^, AM116 ^, EC047, EC015
Controlled Withdrawal	EC015,
Blinded Long Term	EC033 extension

^ a subset of patients had ABPM. Categories are not mutually exclusive.

In the placebo-controlled trials, the demographic distribution of the candesartan treated patients included 39% female, 18% ≥ 65 years of age and only 8% black patients. Demographic distributions are described for each trial in the Medical/Statistical review.

The Medical/Statistical review provides the results for the individual trials. In order to better characterize the dose response relationship, the Med/Stat review includes a Meta-analysis of patients randomized into study AM113, AM116, EC009, EC011, EC018, EC047, EC403, SH-AHM-0001 and AH-AHM-0006. Meta-analysis were also performed to assess the effect on blood pressure in several subgroups. Table EF.2 lists the results from the meta-analysis for DBP and SBP. Pages 261 - 265 in the Med/Stat review outlines the result of the meta-analysis.

Table EF.2. Meta-analysis for Change in DBP and SBP (from Med/Stat review p.261)

Dose (mg)	N	Mean Change in DBP (mmHg)	Mean Change in SBP (mmHg)
0	630	-2.9	-2.5
2	133	-6.6	-10.2
4	352	-7.6	-10.1
8	695	-8.1	-11.3
12	154	-9.3	-14.6
16	347	-9.3	-14.1
32	54	-10.4	-12.1

There is a clear dose response relationship for doses ranging from 2 mg to 16 mg. The curve flattens between 16 and 32 mg. It should be recognized that the estimate for the 32 mg dose is based solely on the data from study AM113. The placebo subtracted mean change in DBP for study AM113 appears to suggest the diastolic blood pressure continues to decline with 32 mg compared to 16 mg (Table EF.3). It should be noted, however, that the effect for 16 mg is less than the 8 mg effect. Thus, there is limited data to support added benefit with the use of 32 mg.

As far as the lowest dose is concerned, 2 mg appears to exhibit a decrease in DBP of 3 to 4 mmHg in the meta-analysis. This effect is driven by the impressive effect in study AM113. Studies EC009 and EC403 show more modest declines in DBP (Table EF.3). Candesartan 4 mg, with the exception of study EC403, consistently lowered DBP by greater than 3 mmHg[11].

Table EF.3. Placebo Subtracted Change in DBP for Selected Placebo-controlled Studies (mmHg).

Dose	AM113 [A]		Study EC009 [B]		Study EC403 [C]	
	N	Δ DBP	N	Δ DBP	N	Δ DBP
0	63	-	39	-	119	-
2	59	-4.7	39	-2.5	41	-2.9
4	62	-5.3	39	-3.1	60	-1.3
8	60	-6.3	39	-3.6	131	-4.2
12			38	-5.3	36	-6.0
16	59	-5.5	39	-5.5		
32	57	-7.9				

[A] from page 80 Med/Stat review.; [B] from page 85 Med/Stat review
[C] factorial study with concerns regarding the validity of data at 6 of 120 centers in Germany; from page 215 Med/Stat review

The sponsor performed a factorial trial (study EC403) with candesartan (2, 4, 8, 16 mg), HCTZ (12.5, 25 mg) and placebo. Normally, this type of study would be viewed as a pivotal study in an application. There are, however, concerns raised by the medical reviewer regarding the conduct of the study. The conduct of the study was tarnished by numerous irregularities as outlined on page 213 of the Med/Stat review. For this reason, it seems reasonable to view this study as supportive information. Table EF.4. and EF.4.a lists the mean change in sitting DBP from baseline to the last blood pressure measurement on therapy.[12]

Table EF.4. Change in siDBP in Study EC403 at Final Measurement.

			Candesartan				
			0	2 mg	4 mg	8 mg	16 mg
HCTZ	0	N	119	41	60	131	36
		Δ siDBP (mmHg)	-4.0	-6.9	-5.3	-8.2	-10.0
	12.5 mg	N	60	45	56	61	39
		Δ siDBP (mmHg)	-5.5	-6.0	-9.9	-10.7	-17.0
	25 mg	N	123	38	64	122	43
		Δ siDBP (mmHg)	-7.4	-7.2	-7.1	-10.2	-12.9

Table EF.4.a. Placebo Subtracted Change in siDBP in Study EC403 at Final Measurement.

			Candesartan				
			0	2 mg	4 mg	8 mg	16 mg
HCTZ	0	N	119	41	60	131	36
		Δ siDBP (mmHg)	-	-2.9	-1.3	-4.2	-6.0
	12.5 mg	N	60	45	56	61	39
		Δ siDBP (mmHg)	-1.5	-2.0	-5.9	-6.7	-13.0
	25 mg	N	123	38	64	122	43
		Δ siDBP (mmHg)	-3.4	-3.2	-3.1	-6.2	-8.9

[11] Study AM113, EC009, EC047 and EC011
[12] 8 week double-blind treatment; last value carried forward

Based on the meta-analysis and the results from the individual studies, 4 mg - 16 mg represents a reasonable dose range for the treatment of hypertension. The effect on SBP appears to be similar to DBP with regard to the shape of the dose response curve. There is insufficient data to support the use of 32 mg because the effect of 32 mg has not been adequately differentiated from 16 mg and there is insufficient long term exposure with 32 mg.

The results from numerous studies (e.g., page 131 Med/Stat review) suggest that the maximum effect on blood pressure is achieved by week 4. There is no significant effect on heart rate.

Response Rate

The response rates for 4 of the placebo-controlled trials are listed in table EF.5. The response rate varies depending on the definition. It is defined two ways:

- diastolic blood pressure < 90 mmHg, or
- diastolic blood pressure < 90 mmHg or change in blood pressure > 10 mm Hg.

Based on the more conservative definition, only 21 - 44% of patients who receive 4 mg will have blood pressure < 90 mmHg and will require additional therapy. For the 16 mg dose, the range is 34 - 58%. The numbers improve dramatically if the less conservative definition is used.

Table EF.5. Response Rate (%) in Placebo-controlled Trials.

Dose	Study EC009		Study EC011		Study AM113		Study EC403	
	< 90	< 90 or Δ ≥ 10	< 90	< 90 or Δ > 10	< 90	< 90 or Δ > 10	< 90	< 90 or Δ > 10
0	15	23	NA	42	20	22	19	30
2 mg	23	44			34	41	22	42
4 mg	21	33	NA	53	44	52	25	38
8 mg	21	41	NA	69	35	47	38	47
12 mg	34	63	NA	58				
16 mg	34	53			45	50	58	69
32 mg					47	56		

< 90 indicates patients who had final measurement < 90 mmHg;
< 90 or Δ > 10 indicates patients who had final measurement < 90 mmHg or change in DBP > 10 mmHg.
NA = not available

To further support the use of a 4 mg dose of candesartan, study EC018 randomized patients to placebo, enalapril 10 mg or candesartan 4 mg for 8 weeks of double-blind treatment. The dose could be doubled at week 4 of treatment if the DBP was > 90 mmHg[13]. In the candesartan group, 62% of the patients did not have the dose doubled.

In another optional dose titration study (AHM0002)[14] that enrolled only type II diabetics, more than half required dose titration from 8 mg to 16 mg. Study AHM004 on patients ≥ 65 years of age also suggested that > 50% of subjects required dose titration from 8 mg to 16 mg. It is unclear if the difference in these studies compared to study EC018 relates to the populations studied.

BID versus OD Dosing

Study AM116 randomized patients to candesartan 8 mg once a day or placebo. After 4 weeks of double-blind treatment, the candesartan patients were force titrated to either candesartan 8 mg BID or 16 mg once a day. As the table on page 160 of the Medical/Stat review indicates, the doubling of dose did not yield any additional decrease in diastolic blood pressure. Because of the failure to show any additional change in DBP with either the BID or once a day dose regimen, the study does not adequately determine whether once a day dosing is similar to BID dosing. The final DBP at week 8 slightly favored BID dosing (Δ 9.7 mmHg BID vs. Δ 9.3 mmHg OD). Dr. Mahjoob was asked to calculate the additional effect of 8 mg BID vs. 16 mg OD in non-responders (DBP > 90 mmHg and Δ < 10 mmHg) at week 4. The additional decrease in DBP after doubling the dose was 5.1 in the BID group and 3.1 mmHg in the once a day group. Recognizing that there are problems associated with drawing conclusions from this type of analysis, it does suggest their may be some benefit with BID vs. once a day dosing in some patients.

[13] enrollment DBP ≥ 95 and ≤ 109 mmHg
[14] enrollment DBP 90 - 100 mmHg

Subgroup Analysis

As with other applications for AII inhibitors, there is inadequate exposure in the black population. The meta-analysis on page 266 and the results from the individual studies[15] clearly suggest that the blood pressure response of black patients is less than the response of white patients.

There does not appear to be a difference in response based on gender or age.

Trough/Peak

Several studies reported trough/peak ratios. Most of these were from studies that measured ABPM in subsets of patients. Some of the reported trough/peak ratios are per protocol analysis rather than intent-to-treat analysis (p. 95 Med/Stat). Further clarification is needed from the sponsor regarding the populations used in the analyses of trough/peak ratios.

Withdrawal Studies

Two studies (EC015, EC040) had a randomized withdrawal to candesartan (+/- amlodipine, +/- HCTZ) or placebo at the end of an open label treatment period. In both studies, the change in blood pressure was less in the candesartan patients compared to placebo (i.e., the placebo patients DBP increased by a greater amount than the candesartan patients). This is suggestive of a long term effect with candesartan therapy.

Active Control Studies

There are six active/and placebo control studies[16] in which single dose regimens of amlodipine or enalapril were included as comparators. Because a dose response for both candesartan and the active agent cannot be calculated, it would inappropriate to compare the effect of the agents for the purpose of declaring that one is superior to the other.

RESOLVD Trial (from Med/Stat Review)

This is a randomized, double-blind, active controlled trial in patients with congestive heart failure. Male and female patients with ejection fraction ≤ 40%, NYHA Class II - IV, 6 minute walk test ≤ 500 meters and ≥ 21 years of age were eligible for randomization. Patients were randomized in a 3:3:1 ratio to candesartan (three dose regimens), candesartan + enalapril (two dose regimens) or enalapril (one dose regimen). The primary measure of efficacy was an assessment of submaximal stress test (6 minute walk test?). An addition endpoint included a determination of the optimum dose regimen of candesartan.

The study randomized 769 patients to 60 centers in the Canada, U.S.A., Italy and Brazil. The study was stopped prematurely by the DSMB and Steering Committee because of the incidence of death was greater in the candesartan group compared to the enalapril group. This difference in death is not statistically significant. Table EF.6 lists the mortality and Mortality + CHF hospitalization for RESOLVD.

Table EF.6. Number of Deaths and CHF Hospitalizations in RESOLVD (from page 257 and 258 Med/Stat review; more event rates are provided in the Med/Stat review)

	Enalapril	Candesartan	Candesartan + Enalapril
N	109	328	332
All Deaths	4 (3.7%)	20 (6.1%)	29 (6.7%)
Death + CHF Hospitalization	7 (6.4%)	42 (14.8%%)	50 (15.1%)

The findings are not impressive for the following reasons:

- The difference in deaths is not impressive because only 3 additional deaths in the enalapril group would essentially wipe out the observation.
- Because both drugs work on the renin-angiotensin system, it would be unexpected to find a significant difference in outcomes. In fact, previous studies in CHF with losartan and captopril (ELITE I) had mortality lower in the losartan group.
- The sample size is too small to make a generalization to the CHF population.
- There is no difference between the candesartan and candesartan + enalapril group. If the results from this trial are believed to be significant, the trial suggests that candesartan has a harmful effect rather than the lack of a beneficial effect.

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[15] study AM113 (page 83),

[16] EC009, EC018, EC033, SH-AHM-0001, AH-AHM-0006, EC011

The results of this study should not be included in the package insert of candesartan.

Safety

Clinical trials were performed in patients with hypertension or CHF in eighteen countries. Deaths and non-fatal serious adverse events from clinical trials in Japan were included but the clinical database and case report forms were not available. Data from 115 patients from 12 centers among eighteen European clinical trials could not be verified and are not included in the safety database. The safety database included data from 5388 patients randomized in 42 studies. All phase II/III trials were conducted in Europe except for three (AM113, AM116, AM119)[17]. Dr. U describes on pages 5 - 12 of his review the types of trials conducted.

The overall number of patients exposed to candesartan cilexetil was 3593 in the original NDA database. Of these, 1946 were enrolled in placebo-controlled monotherapy trials. The duration of exposure as a function of dose is outlined in Dr. U's review on pages 13 - 15. Exposure to 32 mg of candesartan appears to be limited to exposure in study AM113[18] and study AM119.

A safety update submitted on 9/3/97 provided additional information up until 4/30/97. The update included information on one completed study (SH-AHM-0004) and 20 ongoing studies (pp. 19 - 20 Dr. U's review).

Deaths

The clinical program recorded 49 deaths. This includes 17 in the clinical studies in the original NDA submission, 19 in the Japanese clinical trials and 23[19] in the safety update. The treatment assignment for many patients who died are not reported because the studies were still blinded at the time of reporting. Many of the deaths are related to cardiovascular events or cancer and the relationship to candesartan is unlikely. In only one case, candesartan may have contributed to the demise of the patient. For patient 001/551 (study EC403; p. 131 Dr. U's review), candesartan 8 mg was discontinued after 4 days of treatment due to nausea, vomiting and palpitations. Twelve days later the patient had labs performed which showed an abnormal blood urea. She died suddenly 16 days after discontinuing therapy. The relationship of candesartan to the abnormal blood urea and the relationship of the abnormal blood urea to death is not clear.

Adverse Events

Non-fatal serious adverse events occurred in 1.1% of candesartan cilexetil patients and 1.2% of placebo patients in placebo-controlled monotherapy trials. None of the serious adverse events appear to be directly attributable to candesartan monotherapy.

The percentage of patients withdrawn due to adverse events was similar in the candesartan (3.4% and placebo (3.0%) treatment groups in all trials. The adverse event leading to discontinuation may be obscured by the reporting methodology (see section 8.1.3.1, p. 33, Dr. U's review). For patients prematurely withdrawing due to adverse events, all adverse events for that patient during the treatment period, regardless of timing in relation to withdrawal, are included in the listings of adverse events associated with withdrawal from the trial. This has the effect of obscuring the real reason patients discontinued therapy. Headache and dizziness are listed as the most common adverse events in patients who discontinued from therapy. Abnormal liver function tests were reported in 5 candesartan patients (.2%) and no placebo patients. The number of patients prematurely withdrawn due to adverse events does not appear to be a function of dose.

There is no difference between candesartan (48%) and placebo (45%) patients reporting at least one adverse event in all clinical trials. In table 8.1.5-ii-a (p. 40 Dr. U's review), there does not appear to be a dose related increase in the incidence of adverse events[20]. The most common adverse events that occurred with a greater frequency in the candesartan group compared to the placebo group are provided for various sets of trials in Dr. U's review on pages 44 - 54. Dizziness and respiratory related complaints dominate the list (p. 44, table 8.1.5-iv, Dr. U's review). In long term studies, the most common adverse events included multiple respiratory complaints, headache and dizziness (table 8.1.5-xviii, p. 56, Dr. U's review).

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[17] trials beginning with EC were performed by Takeda Euro R + D; trials beginning with SH were conducted by Astra Hassle AB; trials beginning with AM were performed by Astra Merck

[18] see table 5.1.3.2-iii and 5.1.3.2-v on pages 14 - 15 of Dr. U's review

[19] one death in a hypertension trial, 22 deaths in CHF trials

[20] the higher incidence in the > 16 - 32 mg group is difficult to assess because of the small # of patients in this dose range

Lab Data

The lab data only includes information from the original submission. There was no laboratory data included in the safety update. As has been observed with other AII antagonist, the mean hemoglobin and hematocrit decreased slightly (p. 61 Dr. U's review). There was no change in mean creatinine. Potassium increased by .1 mmol/L.

Twelve candesartan and two candesartan/HCTZ patients discontinued from studies due to laboratory abnormalities (p. 66a Dr. U's review). Five of these patients discontinued due to abnormal liver function tests. The liver function test results are not included in the primary review. Additional information on these patients has been requested from the primary reviewer.

There were no significant changes in ECG intervals.

Conclusions

1. Candesartan effectively lowers blood pressure with a total daily dose ranging from 4 mg to 16 mg. There is insufficient safety and efficacy information included in the NDA to support the use of 32 mg.[21] The 2 mg dose was not without an effect on blood pressure but there was not sufficient data to support the use of this dose in hypertension. This may be a reasonable starting dose for the treatment of CHF if the sponsor chooses to pursue that indication.
2. Black patients are under represented in the clinical trials. The effect of candesartan in black patients appears to be less than the effect in white patients. This is similar to the response seen with losartan, eprosartan and irbesartan.
3. The BID dose regimen has been inadequately studied to conclude that BID dosing is not different than once a day dosing. A regulatory decision needs to be made regarding BID statements in the labeling.
4. There are no significant safety concerns specifically associated with this drug product other than those previously identified with this class of drug (e.g., renal insufficiency, angioedema).
5. The results from the RESOLVD trial should not be included in the label. The sponsor should provide an update on the status of other ongoing CHF studies as a condition of approval in order to determine whether there is other evidence of a negative effect on cardiovascular outcomes with candesartan therapy.

Draft labeling has been edited and provided to the project manager.

Charles J. Ganley, M.D.

cc: orig. to NDA
HFD-110 Division File
HFD-110 / Project Manager / C. Ganley /S. Fredd / Khin U / A. Proakis
HFD- 710 / K. Mahjoob
HFD- 810 / J. Piechocki
HFD-860 / A. El-tahtawy / A. Parekh

[21] This is a similar situation to eprosartan. A 1200 mg once a day dose was evaluated in only one study and there was no additional safety data available at the 1200 mg dose. Because of this, a 1200 mg dose of eprosartan was not approved.

BOEHRINGER

JAN 29 1998

Medical and Statistical Review

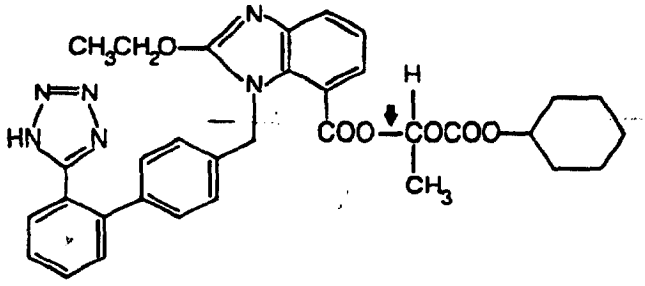
NDA # 20-838

Date of Application: April 30, 1997

Drug Name: Candesartan cilexetil (USAN)
ATACAND™ (Proprietary)

Sponsor: Astra Merck

Structural Formula:



Molecular Formula: $C_{33}H_{34}N_6O_6$

Molecular Weight: 610.67

Chemical Name: (±)-1-(cyclochexyloxcarbonyloxy) ethyl 2-ethoxy-1-[[2'-(1H-tetrazpol-5-yl)biphenyl-4-yl]methyl]-1H-benzimidazole-7-carboxylate

Pharmacologic Category: Angiotensin II (AT_1) Receptor Antagonist.

Proposed Indication: Treatment of Essential Hypertension.

Route of Administration: Oral.

Dosage Form and Strengths: Tablets. 4mg, 8mg, 16mg.

Related Drugs: Losartan, Valsartan, Irbesartan.

Index

1.0 Materials Utilized in Review

The original NDA 20-838, submitted April 30, 1997, contained 498 volumes. Case report forms and tabulations were provided in electronic format and the clinical database was in SAS transport format.

A detailed listing of clinical studies is provided below.

Clinical Pharmacology

Study No.	Objective and Study Design	Treatment / Dosage / Duration
EC001	Double-blind, randomized, placebo-controlled, single rising dose, crossover study. Healthy vols.	CC 0.5mg, 1mg, 2mg, 4mg, 8mg, tablets, oral, once daily; Single dose, 5x Rx periods, 2wks w/o between.
EC001A	Double-blind, randomized, placebo-controlled, single-dose crossover study. Healthy vols.	CC 16mg (2x8mg) tablets, oral, once daily. Single dose, 2x Rx periods, 1 wk w/o between.
EC002	Double-blind, randomized, placebo-controlled, multiple dose crossover study. Healthy vols.	CC 2mg, 4mg, 8mg, tablets, oral, once daily; Single and multiple dose. Rx day 1 and days 3-9, 2 wks w/o between treatment periods.
EC002A	Double-blind, randomized, placebo-controlled, multiple dose crossover study. Healthy vols.	CC 16mg (2x8mg) tablets, oral, once daily; Single and multiple dose. Rx day 1 & days 3-9.
EC008	Double-blind, randomized, placebo-controlled, multiple dose, parallel group study. Healthy vols.	CC 1mg, 2mg, 4mg, 8mg tablets, oral, once daily; 8 days
EC021	Double-blind, randomized, placebo-controlled, multiple dose, crossover study. Healthy vols.	CC 2mg, 4mg, & 8mg tablets, oral, once daily; Single and multiple dose. Rx day 1 & days 3-9, 7 days w/o between.
EC022	Open, single dose PK study in vols with impaired kidney function.	CC 8mg tablet, oral, once daily. 1 day
EC023	Open-label, parallel group, repeated dose study in healthy volunteers & patients with impaired liver function.	CC 12mg tablet, oral, once daily; 6 days (admin once daily on day 1 & days 3-7)
EC026	Double-blind, randomized, placebo-controlled, multiple dose, 2-way crossover study to investigate the PK interaction between CC and an oral contraceptive. Healthy vols.	CC 8 mg tablet, oral, once daily; 2x Rx cycles of 21 days, separated by 7 day w/o.
EC027	Open-labeled, randomized, single dose, 2 way crossover study; Candesartan PK after fasting versus fed state. Healthy vols.	CC 8mg, tablets, oral (taken in fasting & non-fasting state), once daily.; Single dose, 2x dosing periods, at least 1wk w/o between doses.
EC028	Double-blind, randomized, placebo-controlled, 3-way cross-over, HCTZ interaction study; Healthy vols.	CC 12 mg capsule, oral, once daily; HCTZ 25 mg capsules, oral, once daily.; 3 x 7 days
EC032	Open-label, multiple dose, single period, warfarin (W) interaction, PK study; Healthy vols.	CC 16 mg tablet (2x8mg), oral, once daily; W 1 mg tablet, oral, once daily; Dose = 10mg d1, 5mg d2, 4mg d3,4,5, individual adjustment after 30 days W Rx, days 15-24 (10 days) co-admin. of CC.
EC037	Double-blind, randomized, placebo-controlled, multiple dose, 3 way crossover study. Healthy vols.	CC 8mg, 12mg, 16mg capsules, oral, once daily; Single & multiple dose, day 1 & days 3-9, 2 wks w/o between.
EC038	Double-blind, randomized, placebo-controlled, multiple dose crossover study. Healthy vols.	CC 12mg, tablets, oral, once daily; Multiple dose, Rx day 1 & days 3-9, 7 days w/o between.
EC041	Open-labeled, repeated dose, PK & PD study in patients with 3 different levels of kidney function.	CC 12 mg tablets, oral, once daily; 6 days (admin once daily on day 1 & days 3-7)
EC046	Double-blind, randomized, placebo-controlled, single dose, 4-way crossover study. Phase I Healthy male volunteers.	CC 4mg, 8mg, 16mg capsules, oral, once daily. 4 single doses with 6 days w/o between.

Clinical Pharmacology Studies (cont.)

Study No.	Objective and Study Design	Treatment / Dosage / Duration
EC048	Open-labeled, randomized, multiple dose, 3-period, crossover, glibenclamide (G) interaction study. Healthy vols.	CC 16 mg tablet (2x8mg), oral, once daily; G 3.5 mg tablet, oral, once daily; 3 x 7 days
EC051	Open-label, randomized, multiple dose, 3-period, crossover, *nifedipine* (N) interaction study; Healthy vols.	CC 16 mg (2x8mg tablets), oral, once daily N 30 mg sustained release tablet, oral, once daily; 3 x 7 days
EC601	Open label, randomized, multiple dose, 3-way crossover, digoxin (D) interaction study. Healthy vols.	CC 16 mg capsule, oral, once daily. D 0.25 mg tablet, oral, once daily. 3 x 9 days
SH-AHC-0001	Open, randomized, 2-way crossover study. Healthy vols.	8 mg ^{14}C-labeled candesartan cilexetil oral solution 4 mg ^{14}C-labeled candesartan 10 min I.V. infusion. Single doses, 3 weeks w/o.
SH-AHC-0004	Open, randomized, 2-way crossover single dose study. Healthy vols.	CC Astra 16mg tablet, oral; Takeda 2x8mg tablets, oral. Single doses, 1 wk w/o.
SH-AHC-0005	Open, randomized, 2-way crossover single dose study. Healthy vols.	CC 8mg tablet, oral; 8mg solution, oral. Single doses, 1 wk w/o.

Clinical Studies

Study No.	Objective and Study Design	Treatment / Dosage / Duration
AM113	Multicenter, randomized, double-blind, placebo-controlled, dose-response study. HTN pts.	CC 2mg, 4mg, 8mg, 16mg, 32mg, oral, once daily, 4-5 wks placebo run-in, 8 wks double-blind, 2 wk off-drug safety follow-up
AM116	multicenter, randomized, double-blind, placebo-controlled, parallel-design study with an open-label, long-term extension. HTN pts.	CC 8mg tablet, oral, once daily, increased to 8mg bid or 16mg once daily; 8mg or 16mg once daily for open-label evaluation; 4-5 wks placebo run-in, 8 wks double-blind, 2 wk off-drug safety follow-up; 44 wk open-label evaluation
AM119	Randomized, double-blind, placebo-controlled forced dose escalation study. HTN pts.	CC 8mg, 16mg, 32mg, 64mg, oral, once daily, forced dose escalation every 14 days. 4-5 wks placebo run-in, 8 wks double-blind, 2 wk off-drug safety follow-up.
EC009	Double-blind, randomized, placebo-controlled, multiple dose parallel group study (PK part) HTN pts.	CC 2mg, 4mg, 8mg, 12mg, 16mg capsules, oral, once daily. Placebo run-in (2 wks), active Rx (4 wks), placebo run-out (1 wk)
EC011	Double-blind, randomized, placebo-controlled, parallel group study. HTN pts.	CC 4mg, 8mg, 12mg capsules, oral, once daily. E 10mg capsules, oral, once daily. 2-4 wks w/o, 2 wks placebo run-in, 12 wks active Rx
EC012	Open-label, prospective, response-dependent dose titration and a final double-blind comparison with placebo (run-out period). HTN pts.	CC 4mg, 8mg, 12mg, 16mg (4+12mg) tablet, oral, once daily. 4 wks placebo run-in period; 6 month open-label treatment period with response-dependent dose titration; 2 wks double-blind, placebo-controlled, run-out period
EC015	Open-label, prospective, response-dependent dose titration with a randomized double-blind, placebo-controlled withdrawal period. HTN pts.	CC 8mg, 16mg (2x8mg) tablets, oral, once daily; HCTZ 25mg tablet, oral, once daily; Amlodipine 5mg tablet, oral, once daily. 2 wks placebo run-in, 12 wk active Rx, 4 wk withdrawal period
EC016	Open-label, low dose HCTZ Rx followed by prospective, double-blind, randomized, placebo-controlled, 3-way parallel group comparison (baseline HCTZ Rx continued). HTN pts.	CC 4mg, 8mg capsules, oral, once daily HCTZ 12.5mg capsules, oral, once daily 4 wks placebo run-in, 6 wks HCTZ monotherapy, 8 wks double-blind Rx (add-on therapy)
EC018	Double-blind, prospective, randomized, placebo-controlled, 3-way parallel group study. HTN pts.	CC 4mg, 8mg capsules, oral, once daily; Enalapril (E) 10mg & 20mg capsules, oral, once daily; 4 wks placebo run-in, 8 wks active Rx
EC033	Double-blind, randomized, placebo-controlled, multicenter, 5-way parallel group long-term follow-up of EC 011. Additional Rx with HCTZ (12.5 to 25mg once daily) allowed in case of insufficient BP reduction. HTN pts. who completed EC 011.	CC 4mg, 8mg, 12mg capsules, oral, once daily; Enalapril (E) 10mg capsules, oral, once daily; EC 011: 2-4 wks w/o, 2 wks placebo run-in, 12 wks active Rx; EC 033: 40 wks active Rx
EC040	Open-label, prospective, multicenter, response-dependent long-term dose titration, followed by double-blind, placebo-controlled, run-out period. HTN pts.	CC 4mg, 8mg, 12mg, 16mg, oral, once daily. 4 wks placebo run-in; 12 month long-term Rx; 2 wks double-blind placebo-controlled run-out period
EC047	Double-blind, randomized, placebo-controlled, multiple dose, 5-way parallel group, dose finding study. HTN pts.	CC 4mg, 8mg, 12mg, 16mg capsules, oral, once daily; 4 wks placebo run-in, 12 wks active Rx

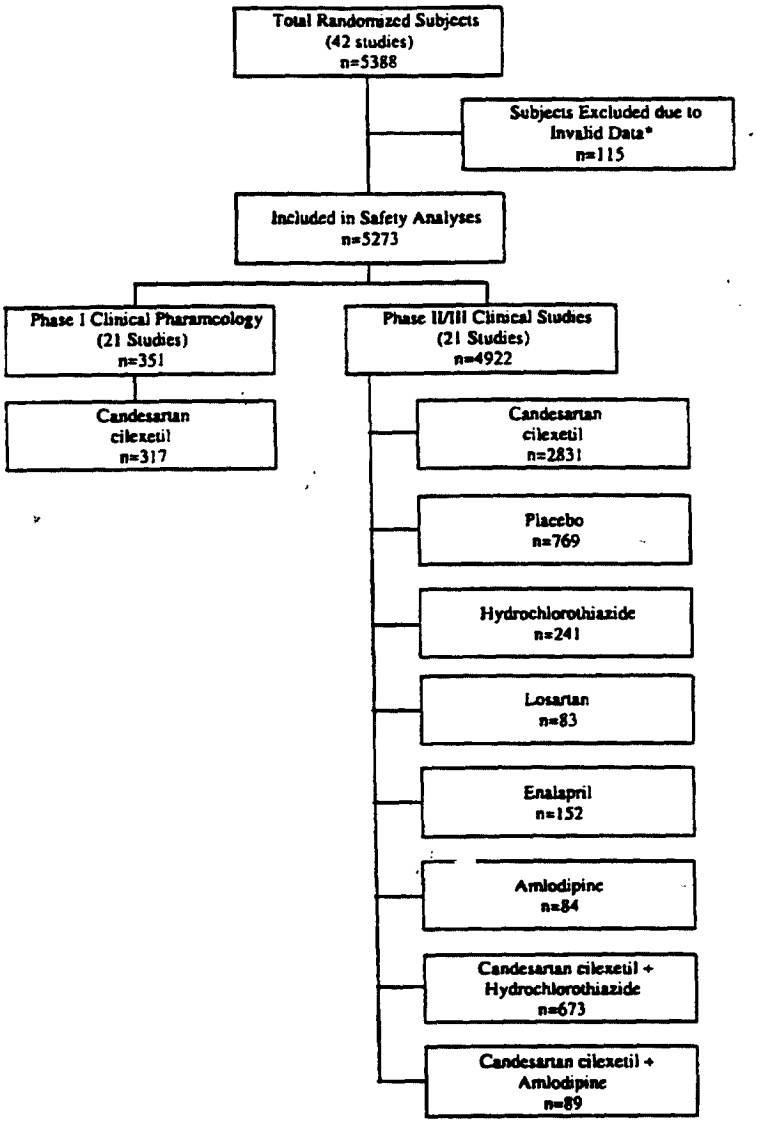
Clinical Studies (cont.)

Study No.	Objective and Study Design	Treatment / Dosage / Duration
EC403	Double-blind, randomized, placebo-controlled, 15 parallel-group factorial study. HTN pts.	CC 2mg, 4mg, 8mg, 16mg (2x8 mg tablets), oral, once daily; HCTZ 12.5mg & 25mg tablets, oral, once daily; + all combinations; 2 wk w/o; 4 wk placebo run-in; 8 wk treatment
EC415	Double-blind, randomized, single dose, parallel group study comparing HCTZ and CC/HCTZ combination. HTN pts.	Combination: CC 16mg (2x8mg)/HCTZ 25mg capsules, oral, once daily. HCTZ 25mg capsules, oral, once daily. Single dose.
SH-AHC-0002	Open-label study, 4 wks placebo run-in. HTN pts.	CC 16 mg tablet, oral. Single dose.
SH-AHC-0003	Double-blind, randomized, parallel group, placebo-controlled titration. HTN pts.	CC 4mg, 8mg, 16mg, 32mg tablet, oral, once day, dose escalation every 3rd day. 14-21 day placebo run-in, 12 days active treatment.
SH-AHC-0007	Single-blind, randomized, parallel group, placebo-controlled dose titration. HTN pts.	CC 16mg, 32mg, 64mg tablet, oral, once day, dose escalation every 3rd day. 14-21 day placebo run-in. 9 days active treatment.
SH-AHM-0001	Double-blind, randomized, placebo-controlled, parallel group, multicenter study. HTN pts;	CC 8mg and 16mg tablets, oral, once daily. Losartan 50mg tablets, oral, once daily. 4 wks placebo run-in, 8 wks active Rx
SH-AHM-0002	Double-blind placebo-controlled randomized parallel group study. Patients with Type II diabetes mellitus. 4 wks placebo run-in. HTN pts.	CC 8mg titrated to 16mg if DBP > 90 mmHg. Oral once daily. 4 wks placebo run-in, 12 wk double-blind
SH-AHM-0006	Double-blind, randomized, parallel group study. HTN pts.	CC 8mg (2x4mg) & 16mg (2x8mg) tablets, oral, once daily. Amlodipine 5mg tablets, oral, once daily. 4 wks placebo run-in, 8 wks active Rx

Studies AHC0002, AHC0003, AHC0007, and EC415 were small safety studies, and are included in the overall safety analysis.

APPEARS THIS WAY
ON ORIGINAL

The original database contained all clinical data received by Astra Merck on or before November 30, 1996. The sum of these clinical data are outlined as follows:



* Invalid patients are those patients for whom data was determined to be fraudulent; and, therefore, was excluded from analyses.

The sponsor amplified this information in the following tables:

Frequencies of Patients Receiving Treatments - All Trials in Patients

Treatment	Number of Patients	Percent of Total
Candesartan Cilexetil	2831	57.5
Placebo	769	15.6
Enalapril	152	3.1
Amlodipine	84	1.7
Losartan	83	1.7
HCTZ	241	4.9
Cand. Cil + HCTZ	673	13.7
Cand. Cil + Amlodipine	89	1.8
Total	4922	100.0

Frequencies of Median Total Daily Dose of Candesartan Cilexetil - All Trials in Patients

Treatment	Number of Patients	Percent of Total Cand. Cil. Patients
Cand. Cil. Monotherapy	2831	78.8
-- > 0 - 2 mg	141	3.9
-- > 2 - 4 mg	560	15.6
-- > 4 - 8 mg	897	25.0
-- > 8 - 12 mg	429	11.9
-- > 12 - 16 mg	714	19.9
-- >16 - 32 mg	90	2.5
Cand. Cil. Combination	762	21.2
-- 2 mg comb.	83	2.3
-- 4 mg comb.	215	6.0
-- 8 mg comb.	366	10.2
-- 16 mg comb.	98	2.7
Total Cand. Cil.	3593	100.0

Cumulative Frequencies for Duration of Exposure to Study Treatment - All Trials in Patients

	Numbers of Patients								Mean	Med
Treatment	≥ 1 d	≥ 1 wk	≥ 2 wk	≥ 4 wk	≥ 8 wk	≥12 wk	≥24 wk	≥48 wk	(days)	(days)
Candesartan Cilexetil Monotherapy	2831	2788	2703	2622	2149	971	452	198	93	58
Placebo	769	763	745	720	573	123	0	0	58	57
Candesartan Cilexetil Combination:	762	744	734	719	579	1	0	0	54	56
-- CC + HCTZ	673	655	645	630	511	1	0	0	53	56
-- CC + amlodipine	89	89	89	89	68	0	0	0	56	56

Since the NDA is for monotherapy, expanded analyses are provided for those trials.

Frequencies of Patients Receiving Treatments - Placebo-controlled Monotherapy Trials

Treatment	Number of Patients	Percent of Total
Candesartan Cilexetil	1946	60.7
Placebo	758	23.6
Enalapril	152	4.7
Amlodipine	84	2.6
Losartan	83	2.6
HCTZ	185	5.8
Total	3208	100.0

Frequencies of Median Total Daily Dose of Candesartan Cilexetil - Placebo-controlled Monotherapy Trials

Dose of Candesartan Cilexetil	Number of Patients	Percent of Total Cand. Cil. Monotherapy Patients
-- > 0 - 2 mg	141	7.2
-- > 2 - 4 mg	352	18.1
-- > 4 - 8 mg	611	31.4
-- > 8 - 12 mg	182	9.4
-- >12 - 16 mg	577	30.0
-- >16 - 32 mg	83	4.3
Total Cand. Cil. Monotherapy	1946	100.0

Cumulative Frequencies for Duration of Exposure to Study Treatment - Placebo-controlled Monotherapy Trials

	Numbers of Patients						Mean	Med
Treatment	≥ 1 d	≥ 1 wk	≥ 2 wk	≥ 4 wk	≥ 8 wk	≥12 wk	(days)	(days)
Candesartan Cilexetil	1946	1928	1910	1868	1477	322	59	57
-- > 0 - 2 mg	141	140	138	132	79	0	46	56
-- > 2 - 4 mg	352	348	345	342	258	71	60	57
-- > 4 - 8 mg	611	605	596	572	465	101	58	57
-- > 8 - 12 mg	182	181	179	179	140	81	67	83
-->12 - 16 mg	577	574	572	565	465	69	59	57
-->16 - 32 mg	83	80	80	78	70	0	55	57
Placebo	758	752	745	720	573	123	58	57

Distribution of Males and Females by Treatment - Placebo-controlled Monotherapy Trials

	Males		Females	
Treatment	n	%	n	%
Cand. Cil.	1192	61.3	754	38.7
Placebo	428	56.5	330	43.5
Enalapril	76	50.0	76	50.0
Amlodipine	55	65.5	29	34.5
Losartan	47	56.6	36	43.4
HCTZ	99	53.5	86	46.5
TOTAL	1897	59.1	1311	40.9

Descriptive Statistics for Age (yrs) - Placebo-controlled Monotherapy Trials

	Age Group								
	<65 yrs		65+ yrs		Total				
Treatment	n	%	n	%	N	Mean	SD	Min	Max
Cand. Cil.	1597	82.1	349	17.9	1946	53.9	10.9	21	87
Placebo	602	79.4	156	20.6	758	54.5	11.2	20	80
Enalapril	134	88.2	18	11.8	152	50.8	11.3	25	75
Amlodipine	69	82.1	15	17.9	84	54.0	11.3	32	76
Losartan	56	67.5	27	32.5	83	59.1	9.4	37	78
HCTZ	144	77.8	41	22.2	185	54.9	11.0	21	75
Total	2602	81.1	606	18.9	3208	54.1	11.0	20	87

Distribution of Blacks and Nonblacks by Treatment - Placebo-controlled Monotherapy Trials

	Nonblack		Black	
Treatment	n	%	n	%
Cand. Cil.	1803	92.7	143	7.3
Placebo	713	94.1	45	5.9
Enalapril	152	100.0	0	0.0
Amlodipine	83	98.8	1	1.2
Losartan	83	100.0	0	0.0
HCTZ	185	100.0	0	0.0
TOTAL	3019	94.1	189	5.9

Subsequent to the original submission the sponsor submitted a safety update on 8/29/97 which included a new controlled clinical study (AHM 004) of 8-16 mg of Candesartan cilexetil or placebo in 350 elderly patients (> 65 years of age) with mild to moderate hypertension (SDBP 95-114 mm Hg) to evaluate the antihypertensive effect and safety of the drug.

On 10/1/97 three new studies were submitted:

1. AM117 - Controlled clinical study of the safety and efficacy of 8-16 mg of Candesartan cilexetil + HCTZ versus placebo + HCTZ in 217 patients with severe hypertension (SDBP ≥ 110 mm Hg).
2. EC058 - PK, hemodynamic effects and safety of 8mg Candesartan cilexetil in 8 hypertensive patients undergoing hemadialysis.
3. EC059 - PK, renal hemodynamic effects and safety of 8 mg Candesartan cilexetil in 24 hypertensive patients with mormal, mild to moderate and severe renal dysfunction.

In addition to the NDA,

were consulted, particularly since a clinical study was stopped early because of safety concerns.

Dr. Steven Caras completed the review of the four clinical studies designated by the sponsor as the primary controlled studies (AM 113, AM 116, AM 119 and SH-AHM-0001). These reviews were incorporated as he finalized them in this document. Dr. Khin U provided a separate review of safety. Consultations were held with chemistry, pharmacology, biopharmaceutics, and others. The data (and most presentations of the data) are the sponsors, but for the metaanalysis.

2.0 Background

Angiotension II's role in regulating arterial blood pressure is outlined in the following figure from Jackson and Garrison in Goodman and Gillman 9th edition.

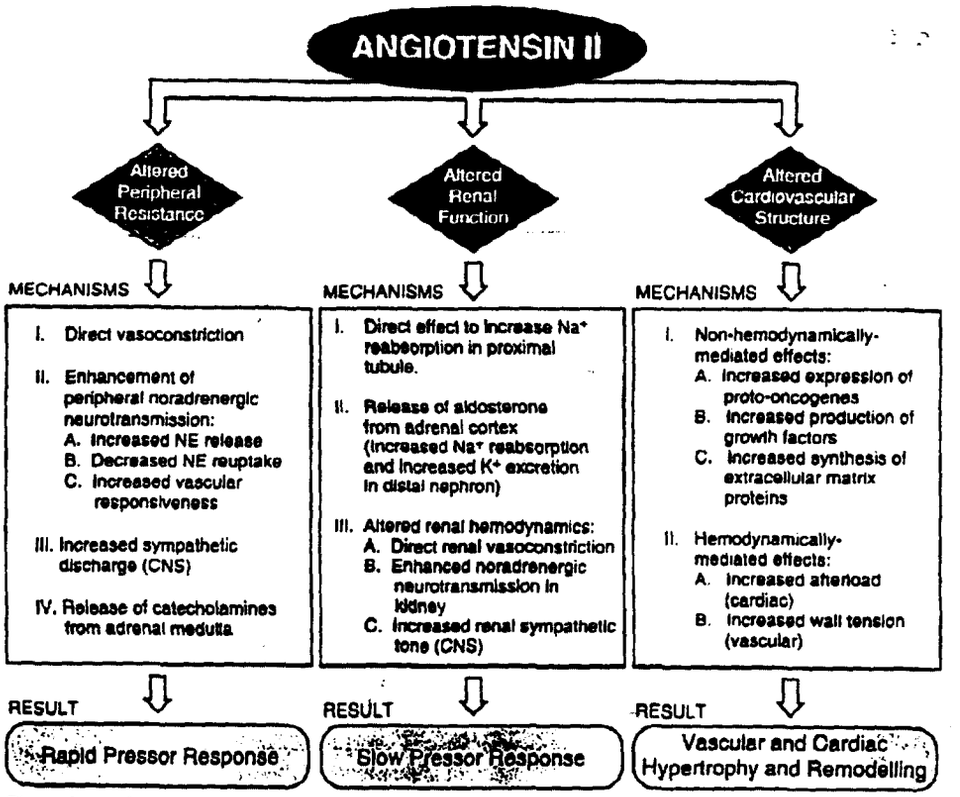


Figure 31–4. Summary of the three major effects of angiotensin II and the mechanisms that mediate them.

Abbreviation: NE, norepinephrine.

ACE inhibitors block the conversion of angiotensin I to angiotensin II. With lower systemic vascular resistance (and other factors) hypertensive blood pressure levels fall without a decrease in renal blood flow. Many ACE inhibitors have been marketed for the treatment of hypertension as well as congestive failure .In CHF patients treated with ACE inhibitors; lower mortality compared to placebo has been noted as detailed in the following chart from Jackson and Garrison's chapter in Goodman and Gillman 9th edition (ibid).

Table 31–1
Summary of Clinical Trials with ACE Inhibitors in Heart Disease

STUDY	REFERENCE	ACE INHIBITOR	PATIENT GROUP	OUTCOME	COMMENT
CONSENSUS	CONSENSUS Trial Study Group, 1987	Enalapril vs. placebo (n = 257)	NYHA IV CHF	Decreased overall mortality	Reduced pump failure
SOLVD-Treatment	SOLVD Investigators, 1991	Enalapril vs. placebo (n = 2569)	NYHA II & III CHF	Decreased overall mortality	Reduced pump failure
V-HeFt II	Cohn *et al.*, 1991	Enalapril vs. hydralazine-isosorbide (n = 804)	NYHA II & II CHF	Decreased overall mortality	Reduced sudden death
SAVE	Pfeffer *et al.*, 1992	Captopril vs. placebo (n = 2231)	MI with asymptomatic LV dysfunction	Decreased overall mortality	Reduced pump failure and recurrent MI
Kleber *et al.*	Kleber *et al.*, 1992	Captopril vs. placebo (n = 170)	NYHA II CHF	Decreased progression of CHF	—
SOLVD-Prevention	SOLVD Investigators, 1992	Enalapril vs. placebo (n = 4228)	Asymptomatic LV dysfunction	Decreased death + hospitalization due to CHF	—
CONSENSUS II	Swedberg *et al.*, 1992	Enalaprilat, then enalapril vs. placebo (n = 6090)	MI	No change in survival	Hypotension following IV enalaprilat
AIRE	AIRE Study Investigators, 1993	Rampril vs. placebo (n = 2006)	MI with overt CHF	Decreased overall mortality	Benefit in 30 days
ISIS-4	ISIS Collaborative Group, 1993	Captopril vs. placebo (n > 50,000)	MI	Decreased overall mortality	Treatment for 1 month
GISSI-3	GISSI-3 Investigators, 1994	Lisinopril vs. open control (n = 19,394)	MI	Decreased overall mortality	Treatment for 6 weeks
TRACE	TRACE Study Group, 1994	Trandolapril vs. placebo (n = 1749)	MI with LV dysfunction	Decreased overall mortality	—
SMILE	Ambrosioni *et al.*, 1995	Zofenopril vs. placebo (n = 1556)	MI	Decreased overall mortality	Treatment for 6 weeks
HOPE and PEACE	Ongoing trials with long-term ACE inhibition in patients with coronary artery disease without ventricular dysfunction and patients at high risk for coronary heart disease.				

NOTE: MI, myocardial infarction; CHF, congestive heart failure; LV, left ventricular; NYHA, New York Heart Association; IV, intravenous administration

Another therapeutic approach to modulate Angiotensin II in hypertension has been the development of Angiotensin II receptor antagonists, particularly affecting the AT_1 receptor subtype. According to Jackson and Garrison,

"*In vitro*, AT_1 receptor antagonists inhibit the contractile effects of angiotensin II in all vascular smooth muscle preparations, and *in vivo*, AT_1 receptor blockers prevent and reverse all the known effects of angiotensin II, including: (1) rapid pressor responses; (2) slow pressor responses; (3) stimulatory effects on the peripheral sympathetic nervous system; (4) all CNS effects (thirst, vasopressin release, sympathetic tone); (5) release of adrenal catecholamines; (6) secretion of aldosterone; (7) all direct and indirect effects of angiotensin II on the kidneys; and (8) all growth-promoting actions. AT_1 receptor blockers reduce arterial blood pressure in animals with renovascular and genetic hypertension as well as in transgenic animals overexpressing the renin gene. AT_1 receptor antagonists, however, have little effect on arterial blood pressure in animals with low-renin hypertension, e.g., deoxycorticosterone acetate-salt hypertensive rats. Most inhibitors demonstrate competitive, surmountable antagonism; however, some demonstrate insurmountable antagonism, a fact that has given rise to the idea that AT_1 receptors may exist in two conformations with different affinities for various antagonists (Robertson et al., 1994). AT_1 receptor antagonists appear to be highly selective. They do not displace ligands that bind to Ca^{2+} channels or adrenergic, muscarinic, dopaminergic, serotonergic, opioid, or neurotensin receptors, and they do not antagonize the actions of vasopressin, catecholamines, acetylcholine, serotonin, bradykinin, or histamine."

Three AT_1 receptor inhibitors (Losartan, Valsartan and Irbesartan) have been approved for the treatment of hypertension. Candesartan cilexetil is another such drug.

2.4 Proposed Labeling

Two key sections state:

INDICATIONS AND USAGE

ATACAND is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents.

DOSAGE AND ADMINISTRATION

The usual starting dose of ATACAND is 16 mg once daily. ATACAND can be administered once daily with total doses ranging from 8 mg to 32 mg. Dosage should be adjusted according to the blood pressure response. The majority of the antihypertensive effect is present within 2 weeks and maximal blood pressure reduction is generally obtained within four to six weeks of ATACAND treatment.

No initial dosage adjustment is necessary for elderly patients, for patients with impaired renal function, or for patients with impaired hepatic function (see CLINICAL PHARMACOLOGY, *Special Populations*). For patients with possible depletion of intravascular volume (e.g. patients treated with diuretics, particularly those with impaired renal function), ATACAND should be initiated under close medical supervision and consideration should be given to administration of a lower dose (see WARNINGS, Hypotension-Volume-Depleted Patients).

ATACAND may be administered with or without food.

If blood pressure is not controlled by ATACAND alone, a diuretic may be added. ATACAND may be administered with other antihypertensive agents.

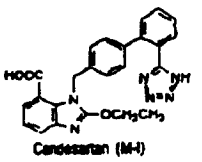
2.5 Foreign Marketing

Marketing applications have been submitted in Europe and Japan. The drug has been approved in the UK for the treatment of hypertension at a starting dose of 4 mg titrated to a maximum of 16 mg once daily.

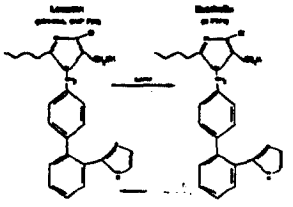
3.0 Chemistry, Manufacturing and Controls

The chemistry review provides the detailed evaluation of the submission. The active drug is candesartan which is liberated from the prodrug candesartan cilexetil by hydrolysis at the gut wall. The proposed metabolic pathway is:

The structure of Candesartan is similar to Losartan, Valsartan and Irbesartan.



Candesartan (M-I)



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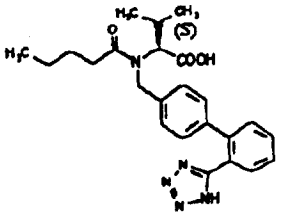
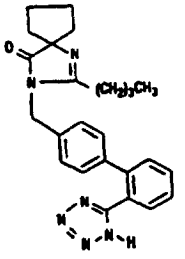
valsartan



Irbesartan



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The cilexetil moiety is liberated as the hydrolysis occurs, and is thought to be absorbed as

It is postulated that cyclohexanol is metabolized as follows:

In 4 mgs of candesartan cilexetil (CCL), there is approximately 1.1 mg of cilexetil (CL); in 8 mg of CCL there is 2.23 mg of CL; in 16 mg, 4.46 mg.

Candesartan itself is achiral and candesartan cilexetil is almost insoluble in water, and slightly soluble in methanol.

Most clinical studies were done with the Takeda product, but one was done with the Astra product, and bioequivalence between the Takeda and Astra products is claimed. The Astra product is the market image.

4.0 Animal Pharmacology and Toxicology

For detailed review of the preclinical studies submitted by the sponsor, see the Pharmacology review. The summary volumes contain the sponsor's overview which may be useful in considering the clinical data that follows. To assist the reader, translations of the following abbreviations are:

TCV-116 = Candesartan cilexetil
MI = Candesartan = CV11974
MI-AG and MI-NG = Candesartan gluconates
MII = Inactive metabolite of Candesartan = CV-15959

Following oral dosing of Candesartan cilexetil, the pharmacokinetic and metabolic profiles of Candesartan in rat, dog, and human were provided in the following chart:

	Species		
	Rat*	Dog*	Human*
Bioavailability (%)	19-28	5	14
Food effect on bioavailability	No	Yes	No
Protein binding (%)	>99	>96	>99
T_{max} (h)	1-4	1-4	4
Mean C_{max} (μg/mL) (at NOAEL or clinical dose)	2.3 (10 mg/kg)	0.09 (20 mg/kg)	0.34 (0.64 mg/kg)
Mean AUC (ug•h/mL) (at NOAEL or clinical dose)	12.3 (10 mg/kg)	0.90 (20 mg/kg)	2.9 (0.64 mg/kg)
Relative exposure ratio	4.2	0.3	1
Urinary recovery ^{14}C (%)	<1	2	33
Fecal recovery ^{14}C (%)	>99	97	68
Plasma metabolites identified	M-I-NG (major)	M-I-NG	(M-II)
Fecal metabolites identified	M-I-AG & (M-II)	M-I-AG & (M-II)	(M-II)
Mean AUC CV-15959 (M-II) (μg•h/mL) (at highest dose)**	59 (10 mg/kg)	72 (10 mg/kg)	0.3 (0.64 mg/kg)
Relative exposure ratio	197	240	1

NOTES: *where available/appropriate data from rats and dogs in the fed state administered TCV-116 orally as a suspension in 5% gum arabic solution and data from humans for an oral dose of 32 mg (0.64 mg/kg assuming a body weight of 50 kg) to hypertension patients using formulated tablets

** subcutaneous administration of CV-15959 (M-II) to rats and dogs; CV-15959 (M-II) formed after an oral dose of 12 mg TCV-116 to healthy male volunteers using formulated tablets

NOAEL = No adverse effect level

Pharmacologic properties of Candesartan cilexetil, Candesartan, and metabolites were evaluated in the following studies.

Study Type	Species
In Vitro Receptor Binding	rabbit, bovine
Pharmacological Effects *In Vitro*	rabbit
Pharmacological Effects Related to Proposed Indication *In Vivo*	rat, dog
Pharmacological Effects of Metabolites	rat, bovine
Pharmacological Effects on Cardiac and Smooth Muscle	guinea pig, rabbit, rat
Pharmacological Effects on Endocrine Function	rat
Pharmacological Effects on the Autonomic Nervous System and Neurohumoral Control	rat, cat, guinea pig
Pharmacological Effects on Respiratory Function	rat
Pharmacological Effects on the Gastrointestinal System	rat
Pharmacological Effects on Neuromuscular Transmission and Skeletal Muscle Function	rat
Pharmacological Effects on Renal Function	rat, dog
Pharmacological Effects on Inflammatory Processes	rat
Pharmacological Effects on the Central Nervous System	mouse, rat, cat

According to the sponsor, in vitro Candesartan inhibited the binding of angiotensin II to rabbit aortic membranes with a K_i of 5.6×10^{-10}, and inhibited angiotensin II contraction of aortic strips. There was slow dissociation from AT_1 receptors.

In vivo, Candesartan cilexetil given orally inhibited angiotensin II pressor response with an ID50 value of 0.07 mg 1 kg, and reduced blood pressure in a hypertensive rat and dog models with a dose response.

In rats Candesartan cilexetil did not affect plasma renin. In pithed spontaneously hypertensive rats, Candesartan affected the pressor response to spinal stimulation. In dogs renal blood flow increased at dose of 3.mg/Kg I.D., but had no effect on heart rate, LV systolic pressure or cardiac output.

There was no GI motility effect or anti-inflammatory effect found in rats.

Some toxicolgic findings in these studies were noted as follows:

Observation of Exaggerated Pharmacology or Toxicity	Dose mg/kg/day	AUC (μg·h/mL)
Decreased heart weight (female)	1 gavage	1.1 - 1.6
Hypertrophy of juxtaglomerular cells	3 gavage	-
Decrease in erythroid parameters Increase in plasma urea nitrogen	10 gavage	2.0 - 2.7
Basophilia of tubular epithelium	100 gavage	13.2 - 15.4
Adrenal, atrophy zona glomerulosa cells	100 diet 600 diet	- -
Stomach, erosion Reticulocyte counts decreased	1000 gavage	-

Single dose acute toxicity studies in mice and rats (observed for 14 days) gave an LD50 of > 2000 mg/Kg of Candesartan cilexetil. In the Beagle dog the lethal dose was > 2000 mg/kg. The LD50 for cyclohexanol in mice and rats was 3.63 and 4.09 g/Kg I.P. respectively. A list of repeat dose toxicity studies was provided as follows:

Test Substance	Species strain	Route	Group Size	Dosage levels (mg/kg)	LD_{50} or Minimum Lethal Dose (MLD) (mg/kg)
candesartan cilexetil	mouse Jcl:ICR	p.o.	5M/5F	500,1000,2000	No signs of toxicity were observed
candesartan cilexetil	dog beagle	p.o.	5M/5F	2000	No signs of toxicity were observed
candesartan cilexetil	mouse Jcl:ICR	i.p.	5M/5F	250,500,1000, 2000	LD_{50}: Males: 807 Females: 891
candesartan cilexetil	rat Jcl:ICR	i.p.	5M/5F	250,500,1000, 2000	LD_{50}: Males: 940 Females: 1210
candesartan & 6 impurities	mouse Jcl:ICR	p.o.	5M/5F	500 &/or 1000, 2000	MLD:1000-2000 for metabolite & 1 impurity, remainder >2000
candesartan	mouse Jcl:ICR	I.V.	5M/5F	910,1180,1540, 2000	LD_{50}: Males: 1120 Females: 1170
candesartan	rat Jcl:ICR	I.V.	5M/5F	910,1180,1540, 2000	MLD: Males: 1180 Females: 1540
M-II (CV-15959)	mouse Jcl:ICR	I.V.	5M/5F	500,1000,2000	MLD: 1000-2000
M-II (CV-15959)	rat Jcl:ICR	I.V.	5M/5F	1000,2000	MLD: 1000-2000
1,2-Cyclo-hexanediol	mouse Jcl:ICR	I.V.	5M/5F	1210,1450,1740, 2080,2500	MLD: Males: 1740 Females: 1450
1,2-Cyclo-hexanediol	rat Jcl:Wistar	I.V.	5M/5F	2410,2890,3740, 4170	MLD: 2890
1,2-Cyclo-hexanediol	mouse Jcl:ICR	i.p.	5M/5F	3760,4130,4170, 4550,5000	MLD: 4130
1,2-Cyclo-hexanediol	rat Jcl:Wistar	i.p.	5M/5F	2890,3470,3790, 4170,4550,5000	MLD: 3470

Test Article	Species/ strain	Route	Duration (Weeks)	Dosage Levels (mg/kg/day)	Group Size
candesartan cilexetil	mouse-Jcl:B6C3F1	p.o. diet	4	1000,3000, 10000	5M/5F
candesartan cilexetil	mouse-Crj:B6C3F1	p.o. diet	13	30,100,300, 1000	10M/10F
candesartan cilexetil	mouse-Slc:B6C3F1	p.o. gavage	13	10,30,100, 300	10M/10F
candesartan cilexetil	rat-Fischer 344/Jcl	p.o. gavage	4	30,100,300	10M/10F
candesartan cilexetil	rat-Fischer 344/Jcl	p.o. gavage	4	1,3,10	10M/10F
candesartan cilexetil	rat-Fischer 344/Jcl	p.o. gavage	4	3000 q.d. or b.i.d.	4M/4F
candesartan cilexetil	rat-Fischer 344/DuCrj	p.o. gavage	4 with 4-13 wk. Recovery	1000,3000	10M/10F 5M/5F/ recovery interval
candesartan cilexetil	rat-Fischer 344/Jcl	p.o. gavage	26	1,10,100, 1000	10/10
candesartan cilexetil	rat-Fischer 344/Jcl	p.o. diet	4	600,2000, 6000	4M/4F
candesartan cilexetil	rat-Fischer 344/Jcl	p.o. diet	13	300,1000, 3000	10M/10F
candesartan cilexetil	rat-Fischer 344/Jcl	p.o. gavage	2	300 with water/saline	5M/5F
candesartan cilexetil	rat-Fischer 344/Jcl	p.o. gavage	4	1000 with water/saline	10M

Test Article	Species/ strain	Route	Duration (Weeks)	Dosage Levels (mg/kg/day)	Group Size
candesartan cilexetil (mechanism)	rat-Fischer 344/Jcl	p.o. gavage	1-4	1000 with water/saline	5-10
candesartan (CV-11974)	rat-Fischer 344/Jcl	I.V.	1	60,200,600	4M
candesartan (CV-11974)	rat-Fischer 344/Jcl	I.V.	4	60,200,600	10M/10F
candesartan (CV-11974)	rat-Fischer 344/Jcl	I.V.	4	60,200,600	3M/3F
candesartan (CV-11974)	rat-Fischer 344/Jcl	I.V.	2	200 with water/saline	5M/5F
M-II (CV-15959)	rat-Fischer 344/Jcl	s.c.	4	1,3,10	10M/10F
candesartan cilexetil & 6 impurities	rat-Fischer DU/Crj	p.o. gavage	2	300	10M/10F
1,2,cyclo-hexanediol	rat-Fischer Jcl:Wistar	i.p.	4	24,20,600	10M/10F
candesartan cilexetil	dog-beagle	p.o. gavage	4	2,4,12,60, 300	3M/3F
candesartan cilexetil	dog-beagle	p.o. gavage	4	20,100,300	3M/3F
candesartan cilexetil	dog-beagle	p.o. gavage	4 with 8 &16 wk. Recovery	300	3-9M
candesartan (CV-11974, M-1)	dog-beagle	I.V.	1	60,200,600	1M/1F
candesartan (CV-11974, M-1)	dog-beagle	I.V.	4	12,60,300	3M/3F

Test Article	Species/ strain	Route	Duration (Weeks)	Dosage Levels (mg/kg/day)	Group Size
CV-15959 (M-II)	dog-beagle	s.c.	4	1,3,10	3M/3F
candesartan cilexetil	monkey-cynomolgus	p.o. gavage	4	2.4,12,60, 300	2M/2F
candesartan cilexetil	dog-beagle	p.o. gavage	26	4,20,100	4M/4F
candesartan cilexetil	dog-beagle	p.o. gavage	52	4,20,100, 300	4M/4F

At 10 mg/Kg/day in the 13 week gavage study in mice, hypertrophy of the juxtaglomerula apparatus and decrease in red cells were noted. At higher doses in dogs basophilia of the renal tubular epithelium and erosion of the gastric mucosa were found. In rats at high doses decreased heart weight, increased BUN, atrophy of the zona glomerulosa of the adrenal cortex, and decreased erythroporetin levels were noted.

In monkeys, rats and dogs liver enzyme increase at oral candesartan cilexetil doses of 300 mg/kg/day, 1000 mg/kg/day and 200 mg/kg/day I.V. of Candesartan respectively.

A battery of reproductive studies were done.

Species/Sex	Study Type	Dose (mg/kg/day)
Rat/M	Fertility; reproductive performance	30, 100, 300
Rat/M,F	Fertility; reproductive performance	10, 50, 300
Rat/F	Teratology dose-ranging	100, 300
Rat/F	Teratology	10, 30, 100
Rat/F	Teratology, supplemental study	300
Rabbit/F	Teratology, dose-ranging	1, 3, 10
Rabbit/F	Teratology	0.3, 1, 3
Rat/F Rabbit/M,F	Teratology, mechanistic study	3 to 100
Mouse/F	Teratology	10, 100, 1000
Rat/F	Peri- and postnatal development	10, 50, 300
Rat/F	Peri- and postnatal development	0.4, 2, 10
Rat/F	Peri- and postnatal development, mechanistic study	300

The sponsor reported hydronephrosis and dilation of the renal pelvis in F_1 animals from damus given more than 2 mg/kg/day from day 15 of gestation. A list of mutagenicity studies was provided:

Study Type	Dose	Test Article		
		TCV-116	CV-11974	M-II
Bacterial mutagenicity - *in vitro*	up to 5000 ug per plate	X		
Bacterial mutagenicity - *in vitro*	up to 5000 ug per plate		X	
Bacterial mutagenicity - *in vitro*	up to 5000 ug per plate			X
Bacterial mutagenicity - *in vitro*	up to 5000 ug per plate	X		
Mammalian mutagenicity - L5178Y cells *in vitro*	1.56 - 100 ug/mL	X		
Mammalian mutagenicity - L5178Y cells *in vitro*	up to 5000 ug/mL		X	
Mammalian mutagenicity - L5178Y cells *in vitro*	up to 5000 ug/mL			X
Mammalian mutagenicity - CHO cells *in vitro*	up to 5000 ug/mL		X	
Mammalian cytogenetics - CHL cells *in vitro*	up to 5 mM		X	
Mammalian cytogenetics - CHL cells *in vitro*	up to 5 mM			X
Mammalian cytogenetics - mouse micronucleus	500, 1000, 2000 mg/kg	X		
Mammalian cytogenetics - mouse micronucleus	500, 1000, 2000 mg/kg	X		
Mammalian cytogenetics - mouse micronucleus	187.5, 375, 750 mg/kg		X	
Unscheduled DNA synthesis - rat hepatocyte	up to 3000 mg/kg	X		

Candesartan and the MII metabolite caused an increased frequency of chromosomal damage in CHL cells in vitro. This was not found in the in vivo mouse micronucleus test.

Oncology studies in rats and mice were said by the sponsor to show no increase in tumor occurrence by the drug compared to control. However, our reviewer of the carcinogenicity studies has found a statistically significant increase in pulmonary tumors in the high dose, female rat group. Further evaluation of this is pending.

5.0 Clinical Pharmacology

27 clinical pharmacology studies of Candesartan cilexetil were submitted. See the Biopharmaceutics review for a comprehensive report of these submitted studies. This presentation will consider studies with clinically relevant findings and 2 healthy volunteer studies for comparison.

The healthy volunteer studies are EC002 and EC002a. These will be referenced to in studies EC021 and EC037 in healthy elderly subjects. Two studies in renally impaired subjects, EC022 and EC041, and one in hepatically impaired subjects, EC023, are included. Two drug-drug interaction studies, one with HCTZ (EC028); one with warfarin (EC032) are presented. Other drug interaction studies were done (digoxin, nifedipine, glibenclamide, and ethinylestrodiol and levonogestrel) but did not show any interaction, and are not presented in this review.

As previously noted, the proposed metabolic pathway for Candesartan cilexetil is:

Candesartan cilexetil is metabolized into the active drug, Candesartan (CV11974) by carbonylesterase which is present in many tissues, but importantly in the gut and liver. Candesartan is metabolized by the liver into an inactive metabolite (CV15959). This pathway involves cytochrome CYP2C9. Cyclohexanol is metabolized (presumably by the liver) into cyclohexanetriol, and rapidly excreted into the urine.

In a human study of Candesartan cilexetil in an oral solution the intact molecule was detected with a C_{max} of 8.6 ng/ml at 0.5 hours after oral ingestion. No intact drug has been detected in human studies when tablets in doses of 0.5-16 mg were used in normals.

The pharmacokinetics of a radiolabeled 8 mg oral alcohol containing solution of Candesartan cilexetil and a 4 mg radiolabeled IV formulation of Candesartan were studied in 8 healthy males with the following results:

Pharmacokinetics of Candesartan and its Inactive Metabolite, MII, After Single Doses of 8 mg ^{14}C-Labeled Candesartan Cilexetil as an Oral Solution and 4 mg ^{14}C-Labeled Candesartan as a 10-min I.V. Infusion.

Parameter	Candesartan	MII (CV-15959)
Oral administration:	mean (SD)	
Absolute bioavailability (%)	42 (6.7)	n.c.
$AUC_{0-\infty}$ (ng x h/mL)	1400 (178)	371 (137)
C_{max} (ng/mL)	233 (45.6)	24.0 (10.8)
t_{max} (h)	1.25 (0.46)	4.00 (0.93)
$t_{1/2}$ (h)	9.3 (3.3)	10.4 (2.1)
Parameter*	Candesartan	MII (CV-15959)
Intravenous administration:		
$AUC_{0-\infty}$ (ng x h/mL)	2320 (293)	371 (32.7)
C_{max} (ng/mL)	997 (178)	23.7 (5.47)
t_{max} (h)	0.20 (0.04)	4.20 (0.83)
V_{ss} (L/kg)	0.13 (0.02)	n.c.
CL (mL/min/kg)	0.37 (0.06)	n.c.
$t_{1/2}$ (h)	9.7 (3.1)	8.65 (0.62)

* mean (SD)
n.c.: not calculated
data from SH-AHC-0001 [Ref(s). 130]

The relative bioavailability of an 8 mg tablet formulation of Candesartan cilexetil was compared to an 8 mg oral solution in 16 healthy males. The tablet relative bioavailability of Candesartan was 34% with the C_{max} of 50.9 ng/ml compared to 271 ng/ml and a T_{max} of 4.3 hours compared to 1.5 hours for the solution.

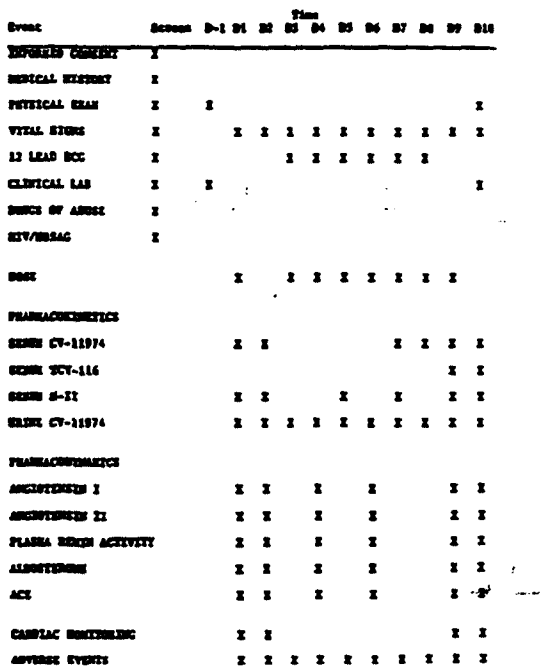
Not only is the bioavailability of Candesartan from tablets low, but once in the circulation it is believed to be 99.8% protein bound (in vitro data) with a "small apparent volume of distribution at steady state (V_{ss} of 0.13L/kg or 9L/70kg) after an I.V. administration." Individual study reports follow.

5.1 Study EC002 - Double-blind, randomized placebo controlled, multiple dose, crossover study in 21 healthy male volunteers to study the PK, PD and safety of Candesartan cilexetil (TCV-116) at doses of 2, 4 and 8 mg Q.D. See also Study EC002a. NDA volumes 1.66 and 1.67.

Dates of Study: October 4, 1992-December 21, 1992.
Randomization: 63 randomization numbers were computer generated. There were 7 treatment sequences. Subjects were assigned as follows:

Sequence	Subject Numbers	Dosing Period 1	2	3
1	4,13,21	2.0 mg	4.0 mg	8.0 mg
2	3,10,16	2.0 mg	8.0 mg	4.0 mg
3	1,12,18	4.0 mg	2.0 mg	8.0 mg
4	7,9,15	4.0 mg	8.0 mg	2.0 mg
5	6,11,20	8.0 mg	2.0 mg	4.0 mg
6	5,14,17	8.0 mg	4.0 mg	2.0 mg
7	2,8,19	Placebo	Placebo	Placebo

Inclusion criteria: male, 18-40 years, within 15% of ideal height for weight, good health.
Exclusion criteria: abnormal chemistry value thought to be clinically significant, smokers of more than 20 cigarettes per day, prescription or OTC drug within 14 days.



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Results

21 subjects were enrolled. 20 subjects completed all assessments. Subject 18 developed a urinary tract infection and did not complete period 3. Subject 8 had an extended washout between periods 2 and 3 due to a dental infection.

Demography: mean age 25.7 years, height 173 cm, weight 70 kg. All were Causcasian. PK results for Candesartan (CV-11974) on day 1 and day 9 were:

Serum CV-11974 Noncompartmental Pharmacokinetic Parameters - Day 1

Mean (Standard Deviation)

Dose Level	N	Cmax (ng/mL)	Tmax (hour)	AUC (ng*hr/mL)	AUC_INF (ng*hr/mL)	MRT (hour)	KEL (1/hour)	t1/2 (hour)
2.0 mg	18	17.27 a (6.52)	3.9 a (0.8)	138.00 a (49.34)	151.59 a (48.25)	9.02 a (2.20)	0.1454 a (0.0369)	5.13 a (1.58)
4.0 mg	18	27.60 b (10.06)	3.6 a (1.0)	222.48 b (63.17)	247.75 b (65.16)	9.41 a (1.83)	0.1336 ab (0.0321)	5.49 a (1.39)
8.0 mg	17	55.00 c (21.65)	4.3 a (1.2)	461.53 c (130.96)	504.37 c (132.09)	9.89 a (1.43)	0.1203 b (0.0165)	5.87 a (0.87)

Note: The Bonferroni multiple comparison procedure was done. In each column means marked with the same letter are not statistically significantly different. Means with different letters are statistically significantly different at the 0.05 level.

Serum CV-11974 Noncompartmental Pharmacokinetic Parameters - Day 9

Mean (Standard Deviation)

Dose Level	N	Cmax (ng/mL)	Tmax (hour)	Cmin (ng/mL)	AUC (ng*hr/mL)	KEL (1/hour)	t1/2 (hour)	MRT (hour)	Cavg (ng/mL)	FLUCT	Accumulation Factor
2.0 mg	18	17.11 a (6.74)	4.0 a (1.6)	6.45 a (0.33)	165.36 a (47.95)	0.1301 a (0.0360)	6.31 a (1.96)	7.23 a (1.33)	6.1 a (2.0)	2.764 a (0.518)	1.16 a (0.62)
4.0 mg	18	30.33 b (12.96)	3.6 a (1.1)	1.31 b (1.09)	290.34 b (75.77)	0.1070 a (0.0377)	7.15 a (2.30)	7.75 a (1.86)	10.0 b (3.1)	2.661 a (0.595)	1.11 a (0.33)
8.0 mg	17	60.48 c (22.33)	3.8 a (1.0)	3.48 c (1.43)	510.98 c (131.77)	0.0990 a (0.0307)	7.30 a (1.59)	7.67 a (0.87)	21.3 c (5.1)	2.609 a (0.546)	1.17 a (0.39)

Note: The Bonferroni multiple comparison procedure was done. In each column means marked with the same letter are not statistically significantly different. Means with different letters are statistically significantly different at the 0.05 level.

Trough concentrations on days 7-10 were:

Mean (Standard Deviation)
(ng/mL)

Dose Level	N	Day 7	Day 8	Day 9	Day 10
2.0 mg	15	0.82 (0.65)	0.99 (0.74)	0.62 (0.61)	1.11 (0.63)
4.0 mg	17	1.71 (1.05)	1.65 (1.34)	1.42 (1.09)	2.43 (0.72)
8.0 mg	17	4.12 (2.10)	4.31 (1.35)	3.50 (1.51)	4.62 (1.21)

Note: The slopes from regressing baseline concentration on day by dose were not significantly different from 0.

PD results for placebo and drug for day 1 and day 9 were:

Baseline Adjusted AUC of Pharmacodynamic Variables Following Placebo

Mean (Standard Deviation)

Visit	Study Day	Plasma Angiotensin I (ng*hr/mL)	Plasma Angiotensin II (pg*hr/mL)	Serum A.C.E. (nmol/min/mL)*hr	Plasma Renin Activity ((ng/mL/hr)*hr)	Aldosterone Concentration (pg*hr/mL)
1	1	5.35 (7.63)	-116.38 (25.25)	-58.32 (48.68)	6.50 (27.83)	-172.35 (320.35)
	9	4.57 (3.99)	-8.75 (20.65)	44.87 (4.99)	32.53 (46.51)	-340.53 (637.74)
2	1	0.00 (0.00)	77.63 (36.01)	267.27 (362.36)	9.95 (-)	-1123.5 (1096.11)
	9	0.00 (0.00)	210.88 (279.86)	178.26 (282.99)	22.85 (16.48)	-1707.1 (1536.91)
3	1	2.13 (3.70)	46.52 (63.99)	-81.06 (8.67)	32.95 (8.48)	-456.18 (580.97)
	9	3.15 (5.63)	131.60 (43.84)	100.15 (71.98)	23.20 (5.09)	-605.02 (1113.62)
Mean	1	2.84 (5.12)	3.44 (105.97)	55.25 (262.29)	9.76 (17.10)	-583.02 (766.83)
	9	2.91 (4.15)	111.04 (161.14)	115.64 (166.31)	27.10 (28.22)	-884.29 (1161.69)

Note: Baseline is the 24-hour AUC of the 0 hour measurement on day 1.

Baseline Adjusted AUC of Pharmacodynamic Variables Following TCV-116

Mean (Standard Deviation)

Study Day	Study Level	Plasma Angiotensin I (ng*hr/mL)	Plasma Angiotensin II (pg*hr/mL)	Serum A.C.E. (nmol/min/mL)*hr	Plasma Renin Activity ((ng/mL/hr)*hr)	Aldosterone Concentration (pg*hr/mL)
1	2.0 mg	7.65 a (11.51)	346.39 a (614.45)	-3.27 a (219.32)	128.28 a (124.10)	95.12 a (616.45)
	4.0 mg	11.15 ab (10.89)	657.15 a (412.39)	-90.18 a (302.13)	146.03 a (124.82)	-35.72 a (724.37)
	8.0 mg	18.39 b (18.04)	826.80 a (970.64)	1.98 a (224.14)	139.01 a (142.00)	-89.13 a (633.78)
9	2.0 mg	12.65 a (13.84)	886.63 a (736.29)	-14.36 a (133.26)	201.03 a (145.25)	457.66 a (855.99)
	4.0 mg	15.49 a (16.66)	1208.66 a (544.64)	10.50 a (154.14)	299.30 a (131.35)	-22.64 a (824.55)
	8.0 mg	40.93 b (37.61)	2604.32 b (1973.36)	-195.94 a (630.95)	371.21 a (309.55)	228.70 a (920.47)

Note: Baseline is the 24-hour AUC of the 0 hour measurement on day 1.
In each column means marked with the same letter are not statistically significantly different. Means marked with different letters are statistically significantly different at the 0.05 level from the F-test for treatment effect in ANOVA (Appendix 8.12).

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The effect on blood pressure for placebo and drug were:

Baseline Adjusted 2 to 16 Hour Mean Blood Pressure Following Placebo

(mmHg)

Dosing Period	Day	N	Supine Systolic	Supine Diastolic	Sitting Systolic	Sitting Diastolic
			By Visit			
1	1	3	4.1	7.5	0.9	-0.8
	9	3	-1.7	-5.2	-1.2	-2.2
	Mean	6	1.2	1.1	-0.2	-1.5
2	1	3	8.2	0.5	3.7	1.6
	9	3	-9.4	-3.6	-4.7	-0.1
	Mean	6	-0.6	-1.6	-0.5	0.8
3	1	3	7.0	11.5	7.5	8.8
	9	3	-2.3	3.0	-1.9	0.4
	Mean	6	2.3	7.2	2.8	4.6
			By Day			
1	1	3	4.1	7.5	0.9	-0.8
2		3	8.2	0.5	3.7	1.6
3		3	7.0	11.5	7.5	8.8
	Mean	9	6.4	6.5	4.0	3.2
1	9	3	-1.7	-5.2	-1.2	-2.2
2		3	-9.4	-3.6	-4.7	-0.1
3		3	-2.3	3.0	-1.9	0.4
	Mean	9	-4.5	-2.0	-2.6	-0.6

Note: Mean 2-16 hour AUC is adjusted for the 0 hour measurement on day 1.

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Baseline Adjusted 2 to 16 Hour Mean Blood Pressure Following TCV-116

(mmHg)

Study Day	Dose Level	N	Supine Systolic	Supine Diastolic	Sitting Systolic	Sitting Diastolic
1	2.0 mg	18	0.7	-1.7	-0.1	-2.2
	4.0 mg	18	4.5	0.4	4.0	-1.1
	8.0 mg	17	2.2	-3.0	-0.3	-2.8
9	2.0 mg	18	4.2	-4.8	4.7 a	-3.3
	4.0 mg	18	0.2	-4.8	0.4 ab	-3.1
	8.0 mg	17	-1.1	-5.1	-1.3 b	-4.4

Note: Mean 2-16 hour AUC is adjusted for the 0 hour measurement on day 1.
In each column by study day, means marked with different letters are significantly different from each other at the .05 level from ANOVA (Appendix 8.4).

Safety

No deaths or serious adverse events were reported. As previously noted, one subject withdrew for a urinary tract infection before period 3.

Headache was the most frequently reported complaint, occurring in all groups. Numerical shifts in laboratory values occurred in the placebo and active drug groups, none of which indicated a clinical problem. ECGs remained normal in all cases.

5.2 Study EC002a - Double-blind, randomized, placebo controlled, multiple dose study in 17 healthy male volunteers to study PK, PD and safety of Candesartan cilexetil (TCV-116) at a dose of 16 mg Q.D.

NDA Volume 1.68
Dates of Study: January 12. 1993-January 28, 1993.
This study done at the same center by the same PI was a follow-up to EC002 following identical procedures to add results for a 16 mg dose to the data already obtained for 2, 4 and 8 mg.
Randomization: 20 randomization numbers were generated and subjects assigned to one of the dosing regimens as follows:

Dose Level	Subject Number
16.0 mg	1. 2. 4. 5. 6. 8. 9. 10. 11. 13. 14. 16. 17*
Placebo	3. 7. 12. 15

*Replacement number

Results

17 subjects were enrolled. Subject 2 withdrew on day 6 "for personal reasons," and was replaced by subject 17.
Demography: mean age was 26.8, height 175.1 cm, weight 72.6 kg. All were Caucasian.
The PK/PD results for the 16 mg dose were presented with the results for 2, 4 and 8 mg from study 002:

Combined Serum CV-11974 Pharmacokinetic Parameters

Mean (standard Deviation)

Dose Level	Sex	N	Cmax (ng/dL)	Tmax (hour)	Cmin (ng/dL)	AUC (ng*hr/mL)	AUC_INF (ng*hr/mL)	KEL (1/hour)	t1/2 (hour)	MRT (hour)	CLss (L/hr/kg)	Vss/F	Accumulation Factor
2.0 mg	1	10	17.27 (8.54)	1.0 (0.0)		136.00 (66.24)	151.59 (68.95)	0.1454 (0.0360)	5.13 (1.96)	9.02 (2.80)			
	0	10	17.11 (8.74)	0.0 (1.6)	0.45 (0.53)	145.10 (67.95)		0.1202 (0.0368)	6.31 (1.96)	7.23 (1.33)	6.1 (2.0)	2.764 (0.510)	1.16 (0.02)
4.0 mg	1	10	37.60 (18.06)	1.0 (1.0)		222.88 (63.17)	247.75 (65.14)	0.1336 (0.0321)	5.69 (1.39)	9.41 (1.01)			
	0	10	39.33 (18.04)	3.6 (1.4)	1.31 (1.00)	260.34 (75.37)		0.1070 (0.0377)	7.15 (2.30)	7.75 (1.06)	16.0 (3.3)	2.661 (0.595)	1.11 (0.33)
8.0 mg	1	17	55.08 (21.65)	0.1 (1.2)		461.53 (150.96)	504.17 (132.09)	0.1203 (0.0365)	5.87 (0.87)	9.09 (1.42)			
	0	17	60.46 (20.33)	3.8 (1.0)	2.08 (1.02)	510.90 (121.77)		0.0990 (0.0301)	7.30 (1.59)	7.67 (0.87)	21.3 (5.1)	2.609 (0.548)	1.17 (0.39)
16.0 mg	1	12	107.5 (39.96)	2.6 (0.8)		1063.63 (319.24)	1107.11 (330.38)	0.1196 (0.0300)	5.96 (1.10)	11.14 (1.08)			
	0	12	119.2 (42.84)	4.0 (1.3)	5.17 (2.36)	1016.79 (870.45)		0.1044 (0.0330)	6.96 (1.67)	9.01 (1.13)	42.0 (11.5)	2.692 (0.398)	1.02 (0.34)

Combined AUC of Pharmacodynamic Variables

Mean (Standard Deviation)

Dose Level	Day	Plasma Angiotensin I (pg*hr/mL)	Plasma Angiotensin II (pg*hr/mL)	Serum A.C.E. (nmol/min/mL)*hr	Plasma Renin Activity ((ng/ml/hr)*hr)	Aldosterone Concentration (pg*hr/mL)
2.0 mg	1	13.78 (10.33)	746.07 (687.22)	2828.06 (595.56)	164.02 (138.28)	1180.19 (673.05)
	9	18.79 (10.26)	1086.31 (803.77)	2816.96 (634.36)	236.76 (153.11)	1542.73 (829.50)
4.0 mg	1	17.28 (12.49)	808.63 (464.87)	2718.83 (601.95)	179.21 (125.63)	1090.22 (618.52)
	9	21.63 (16.02)	1337.17 (829.68)	2819.11 (607.55)	241.76 (129.54)	1141.31 (538.17)
8.0 mg	1	21.40 (17.43)	986.28 (927.67)	2898.28 (585.26)	153.74 (148.60)	988.05 (675.97)
	9	43.78 (34.78)	2776.53 (1865.38)	2700.17 (630.79)	371.36 (311.32)	1305.87 (562.77)
16.0 mg	1	23.70 (16.56)	858.45 (499.54)	2386.20 (480.21)	206.65 (114.12)	975.87 (496.71)
	9	46.20 (17.50)	2019.43 (1267.08)	2435.82 (436.44)	445.75 (210.65)	1376.44 (467.66)

Note: Dose levels 2.0 mg to 8.0 mg were from previous study EC002.

Blood pressure results for placebo and the active subjects were:

Baseline Adjusted 2 to 16 Hour Mean@ Blood Pressure

(mmHg)

Dose Level	Day	N	Supine Systolic	Supine Diastolic	Sitting Systolic	Sitting Diastolic
Placebo	1	4	9.6	1.8	11.4	2.6
	9	4	7.1	-0.3	0.2	-4.1
	Mean		8.3	0.8	5.8	-0.8
16.0 mg	1	12	4.8	-1.5	5.4	2.1
	9	12	-3.2	-4.3	-2.0	-4.8
	Mean		0.8	-2.9	1.7	-1.3

Note: @ Mean 2-16 hour AUC is adjusted for the 0 hour measurement on day 1.

Safety

No deaths, serious adverse events or adverse events leading to withdrawal were reported. Headache was the most frequent complaint in both groups. Rash, fatigue were also reported. ECGs were reported abnormal (slight left axis deviation) post study for 2 placebo subjects. Chemistries changed in both placebo and active drug. For both groups there was a decline in bilirubin, hemoglobin, hematocrit and erythrocytes. In Candesartan subjects there were slight increases in ALT, creatinine, leukocytes and ESR.

5.3 Study EC022: Pharmacokinetic study of Candesartan cilexetil (TCV-116) after an 8 mg single oral dose in 6 volunteers with moderate renal impairment. (See also EC041).
NDA Volume 1.78
Centers: University Hospital Antwerp and Bio Pharma Research Unit, Antwerp, Belgium.
Investigators: Drs. De Broe and Lins.
Study Period: September 1993-July 1994.
Drug:
Inclusion Criteria: 18-65 years, stable creatinine clearance between 20-50 L/min/ $1.73m^2$, normotensive or mild hypertension (sitting DBP < 105 mm Hg).
Exclusion Criteria: pregnancy, severe cardiac disease, diabetes.

This was an open, single dose study. Blood samples were taken for 30 hours for 4 subjects, 48 hours for 2 subjects, urine for 48 hours after an overnight fast and admission to the center. Analysis for Candesartan cilexetil (TCV-116), Candesartan (CV-11974) and its inactive metabolite (CV-15959) were done.

Results

6 subjects, 54 to 70 years, 4 males, 2 females were studied. Up to a 2 µg/ml level of detection, TCV-116 was never detected. For Candesartan and its inactive metabolite the results were:

Table 1 : Pharmacokinetic parameters derived from serum concentration profiles of CV-11974 and CV-15959 obtained after a single dose administration of 8 mg of TCV-116 in moderate renal impaired subjects.

Parameter	CV-11974	CV-15959	N
Cmax (ng/mL)	114 (64.6-174)	10.9 (6.67-20.5)	6
Tmax (h)	4 (3-6)	12 (8-30)	6
AUCt (ng.h/mL)	1386 (739-2891)	298 (165-664)	6
AUCe (ng.h/mL)	1696 (839-5685)	651 (416-850)	4
MRTe (h)	18.0 (13.4-43.7)	42.8 (33.4-69.2)	4
T½el (h)	13.4 (9.5-31.4)	25.1 (18.9-45.2)	4

Values are median (range) for Tmax and geometric mean (range) for other parameters

Safety

There were no deaths, serious adverse reactions or withdrawals. One subject had dizziness, another headache.

5.4 Study EC041: Pharmacokinetics, renal hemodynamic effects and safety of Candesartan cilexetil (12 mg Q.D.) in hypertensive patients with A) normal renal function, B) mild to moderate renal dysfunction, and C) severe renal dysfunction.
NDA Volume 1.78
Single Center: Mario Negri Institute, Bergamo, Italy.
Principal Investigator: G. Ramuzzi, M.D.
Dates of Study: June 28, 1995-February 15, 1996.
Open label, parallel group, 24 patient study.
Inclusion Criteria:

Mean DBP 90-109 mm Hg one week prior to drug administration.
Ages 18-65 years
Males or females (non-child bearing potential).
Group A. GFR>60 ml/min/1.73m^2 - normal renal function.
Group B. GFR 31-60 ml/min/1.73m^2 - mild to moderate renal dysfunction.
Group C. GFR 15-30 ml/min/1.73m^2 - severe renal dysfunction.

Exclusion Criteria:

Severe other organ disease
Hemodialysis
Potassium > 5.5 mEq/l
GI surgery
Liver disease, enzymes > 2x ULN.

Stable maintenance therapy with furosamide, digoxin, aluminum oxide, vitamins, lactulose, calcium or other supplements were permitted.
The flow chart for the study was:

ACTION	SCREENING AND WASHOUT		TREATMENT PERIOD AND OBSERVATION PERIOD										POST-STUDY CHECK
Study day	-14 to -2	-1	1	2	3	4	5	6	7	8	9	10	10 to 14
Inclusion/exclusion criteria	x	x											
Medical History	x												
Physical examination	x												x
Vital signs (BP, pulse rate)	x			x	x	x	x	x	x	x	x	x	
ECG	x												x
Routine hematology, biochemistry, urinalysis	x												x
Creatinine clearance*, urinary sodium excretion		x											
Adverse events			x	x	x	x	x	x	x	x	x	x	x
Drug administration			x		x	x	x	x	x				
Blood sampling for pharmacokinetics			x	x	+	+	+	+	x	x	x	x	
Renal hemodynamics: Inulin/PAH clearance		x							x				

+ = trough serum levels of candesartan

* Creatinine clearance as an estimate of GFR was only determined on day -1 as inclusion criterion.

Initially 24 patients were supposedly completed. An audit found that data from 16 patients were unreliable. The study was redone with a new cohort of 24 patients under supervision of a different co-investigator. The data of 8 patients found to be reliable data was included for safety analysis.

The demographic data for the 24 second cohort were:

		Group A		Group B		Group C	
		male (7)	female (1)	male (7)	female (2)	male (5)	female (2)
Age (years)	Mean	46.2	62.2	51.9	51.4	55.7	44.0
	Range						
Height (cm)	Mean	174.9	152.0	171.0	159.0	174.2	164.0
	Range						
Weight (kg)	Mean	82.9	50.0	79.8	57.3	81.1	56.5
	Range						
Race	White	7	1	7	2	5	2
	Black	0	0	0	0	0	0
	Oriental	0	0	0	0	0	0
	Other	0	0	0	0	0	0
Creatinine clearance (ml/min/1.73 m² BS)	Mean	103		45.8		21.9	
	Range						

- Patients 25 - 36 and 41 to 52 considered for statistics
- geometric mean of creatinine clearance

The Candesartan results were:

	Group A		Group B		Group C	
	Day 1	Day 7	Day 1	Day 7	Day 1	Day 7
$t_{1/2}$ (h)*	11.8	12.3	12.2	17.3	14.3	20.7
C_{max} (ng/ml)	109	106	161	151	147	170
t_{max} (h)*	4.3	3.6	3.9	3.6	3.9	3.3
$AUC_{0-\infty}$ (ng*h/ml)	1209	1373	1926	2465	2280	3905
AUC_{tau} (ng*h/ml)	-	1062	-	1600	-	2238
R_{ac}	-	1.14	-	1.28	-	1.71
R_{ain}	-	0.88	-	0.83	-	0.98

Arithmetic means of differences or geometric means of ratios of pharmacokinetic parameters of CV-11974, and 2-sided 90% confidence intervals (CI). Between-group evaluation

Day 1:

$t_{1/2}$ (h)	mean	90% CI		signific.
group B - group A	0.35	-2.2	2.9	N
group C - group A	2.5	-0.20	5.7	N
group C - group B	2.1	-0.48	4.8	N
C_{max} (ng/ml)	mean	90% CI		signific.
group B / group A	1.49	1.16	1.91	Y
group C / group A	1.35	1.04	1.76	Y
group C / group B	0.91	0.70	1.18	N
t_{max} (h)	mean	90% CI		signific.
group B - group A	-0.36	-2.2	1.5	N
group C - group A	-0.39	-2.3	1.9	N
group C - group B	-0.03	-1.9	1.9	N
AUC_{0-t} (ng.h/ml)	mean	90% CI		signific.
group B / group A	1.59	1.12	2.26	Y
group C / group A	1.89	1.30	2.73	Y
group C / group B	1.18	0.83	1.70	Y

Day 7:

$t_{1/2}$ (h)	mean	90% CI		signific
group B - group A	5.0	-0.55	11.	N
group C - group A	8.4	2.5	14.	Y
group C - group B	3.4	-2.4	9.2	N
C_{max} (ng/ml)	mean	90% CI		signific
group B / group A	1.42	1.08	1.87	Y
group C / group A	1.60	1.19	2.14	Y
group C / group B	1.12	0.85	1.50	N
t_{max} (h)	mean	90% CI		signific
group B - group A	-0.01	-0.90	0.87	N
group C - group A	-0.34	-1.3	0.61	N
group C - group B	-0.33	-1.2	0.60	N
AUC_{0-t} (ng.h/ml)	mean	90% CI		signific
group B / group A	1.51	1.04	2.18	Y
group C / group A	2.11	1.42	3.12	Y
group C / group B	1.40	0.95	2.05	N
$AUC_{0-\infty}$ (ng.h/ml)	mean	90% CI		signific
group B / group A	1.80	1.22	2.64	Y
group C / group A	2.84	1.89	4.28	Y
group C / group B	1.58	1.06	2.36	Y
R_{ac}	mean	90% CI		signific
group B / group A	1.13	0.90	1.41	N
group C / group A	1.51	1.19	1.92	Y
group C / group B	1.34	1.06	1.69	Y
R_{ss}	mean	90% CI		signific
group B / group A	0.95	0.74	1.21	N
group C / group A	1.12	0.86	1.45	N
group C / group B	1.18	0.92	1.52	N

signific.: Y = significant difference , N = non-significant difference

The free fraction of Candesartan was determined:

Group A		Group B		Group C	
Day 1	Day 7	Day 1	Day 7	Day 1	Day 7
0.562	0.542	0.703	0.705	0.783	0.754
0.55*		0.70*		0.77*	

* = Arithmetic mean (pooled results)

Geometric means of the ratios, and 2-sided 90% confidence intervals (CI), of CV-11974 serum concentrations unbound to serum.
Between-group evaluation.

	day 1				day 7			
	mean	90% CI		signific.	mean	90% CI		signific.
group B / group A	1.25	0.94	- 1.67	N	1.30	1.00	- 1.70	N
group C / group A	1.39	1.03	- 1.89	Y	1.39	1.05	- 1.85	Y
group C / group B	1.12	0.83	- 1.50	N	1.07	0.81	- 1.41	N

signific.: Y = significant difference from unity, N = non-significant difference

Safety

No deaths, serious adverse events or withdrawals for adverse events were reported. One patient (initial cohort) reported a headache. Another patient (second cohort) had isolated supraventricular extrasystoles.

Laboratory findings did not worsen from baseline. PAH insulin clearance and filtration fraction were determined on day 1 and day 7. There was a significant decrease in filtration fraction over that time for the severe renal dysfunction group (C).

5.5 Study EC023: Comparison of pharmacokinetics and safety of Candesartan cilexetil (TCV-116) 12 mg Q.D. for 7 days in subjects with and without impaired hepatic function.
NDA Volume 1.77
Single Center: Christian Albrechts University, Kiel, Germany.
Principal Investigator: W. Kirch, M.D.
Study Period: December 10, 1994-January 23, 1995.
Protocol amendment December 16, 1994 increased sample size from 10 to 12.
Drug manufactured by

Inclusion Criteria: Males or females, 18-75 years.
Liver dysfunction group: Status 14 days prior to 1st dose - mild to moderate liver disease, e.g. fatty liver or hepatitis but not cirrhosis, chronic active hepatitis, or shunting. Liver disease determined by SGOT, SGPT, γGT, antipyrine clearance 10-35 ml/mm, and sonogram or biopsy.
Normals - matched by sex, age and weight as far as possible.

Exclusion criteria included:
- severe cardiac disease
- suspected renal impairment (creatinine > 1.8 mg/dl).
- abnormal serum potassium
- gastrointestinal surgery

Flow chart of the study:

Assessment	SCREENING AND WASH-OUT	TREATMENT PERIOD*									FOLLOW-UP
Study day	-14 to -1	1	2	3	4	5	6	7	8	9+	9 to 15
In-/exclusion criteria	x										
History	x										
Physical examination	x										x
Vital signs and ECG	x										x
Routine hematology, biochemistry, urinalysis	x										x
Adverse events		x	x	x	x	x	x	x	x	x	x
Drug administration		x		x	x	x	x	x			
Blood sampling for pharmacokinetics		x	x	x ◆		x ◆	x ◆	x	x	x	
Liver function tests	x										

* trough serum levels of candesartan (CV-11974)
† Subjects were hospitalised on days 1 and 7, whereas they were ambulant on the other study days
◆ Blood sample on day 9 = 48-hour sample of day 7.

Results

12 healthy subjects and 13 with impairment enrolled. One patient with liver impairment withdrew on day 3. Results for PK include 12 normals and 12 patients. All 25 cases were included in the safety analysis.

Demographic comparisons were:

		Liver impaired patients (n = 13)*	Healthy volunteers (n = 12)
Age (years)	Mean Range	51 5 31-71	46 3 32-71
Height (cm)	Mean Range	176 164-191	173 4 165-180
Weight (kg)	Mean Range	78 7 59-99	68 8 59-85
Race	White	13	12

* one subject was withdrawn from the study

Hepatic enzyme and antipyrine comparisons were:

Healthy volunteers (n=12)

	Transaminases SGOT (U/l)	SGPT (U/l)	γ-GT (U/l)	Antipyrine clearance Calculated antipyrine clearance (ml/min)
Range				
Mean	8 8	9 7	10 2	39 5
Median	8 6	9 2	9 3	37 9

Liver impaired patients (n=12)*

	Transaminases SGOT	SGPT	γ-GT	Antipyrine clearance Calculated antipyrine clearance (ml/min)
Range				
Mean	26 6	36 3	72 8	21 6
Median	22 0	34 2	56 1	22 1

* n = 13 were enrolled, one subject was withdrawn from the study and not evaluated for pharmacokinetics. For this reason, results of liver diagnosis are summarised for the 12 subjects evaluable for pharmacokinetics

Sonography result was "fatty liver" in all hepatic cases and was "normal" in healthy volunteers.

PK results day 1 were:

LIVER IMPAIRED PATIENTS

	Arithmetic					Geometric		
	Mean	SD	95% C.I. of the mean lower - upper	Median	75% percentile	Mean	SD	95% C.I. of the mean lower - upper
$T_{1/2}$(h)	12	8.3	8.4 - 15	10.5	14			
C_{max} (ng/ml)						109	40.1	87.1 - 137
T_{max} (h)	2.7	0.85	2.3-3.0	2.5	3.0			
AUC_t(ng.h/ml)						881	334	696 - 1112
AUC_{∞} (ng.h/ml)*						1030	483	776 - 1367
AUC_{∞} (ng.h/ml)						1107	560	818 - 1499
MRT_{po}(h)						11	3.2	9.0 - 13

*: t = timepoint of last measurable concentration above blq

HEALTHY VOLUNTEERS

	Arithmetic					Geometric		
	Mean	SD	95% C.I. of the mean lower - upper	Median	75% percentile	Mean	SD	95% C.I. of the mean lower - upper
$T_{1/2}$(h)	9.3	2.7	7.5 - 11	9.4	11			
C_{max} (ng/ml)						95.2	29.9	78.4 - 116
T_{max} (h)	3.0	1.4	2.2 - 3.9	2.5	3.2			
AUC_t(ng.h/ml)						706	314	541 - 927
AUC_{∞} (ng.h/ml)*						864	388	703 - 1062
AUC_{∞} (ng.h/ml)						909	397	737 - 1120
MRT_{po}(h)						11	2.7	9.3 - 12.8

*: t = timepoint of last measurable concentration above blq