

5/17/02

To: NDA 20838, SE 4-015
From: Stephen Fredd, HFD-110
Subject: Medical Review

BACKGROUND

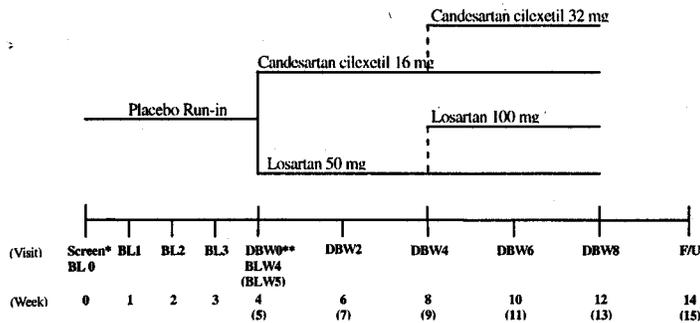
On 9/27/2001 AstraZeneca submitted a supplement to their approved NDA for Candesartan cilexetil to add statements in the **Clinical Trials, Clinical Pharmacology and Overdose** sections of the labeling. They propose incorporating the results of studies 230 and 231 (the CLAIM studies) to provide comparative efficacy information of Candesartan to losartan in the **Clinical Trials** section. The **Clinical Pharmacology** section would be amended to include new data on PK in hepatically impaired individuals with a recommendation for consideration of a lower starting dose. The **Overdose** section would be revised to delete the case report of the one overdose patient currently described, and include the “most clinically useful information” derived from a review of all overdose cases received between October 1996 and October 2000. Volumes 1.1, 1.4, 1.5-1.85 and electronic submissions of the case report tabulations and case report forms were provided for the medical review.

COMPARATIVE EFFICACY

The CANDLE study (protocol 175) and the Claim studies (protocols 230 and 231) provide the basis for the sponsor’s claim that “Candesartan cilexetil initiated at 16 mg once-daily and forced-titrated at 2 weeks to 32 mg once-daily was statistically significantly more effective than losartan 50 mg once-daily forced-titrated at 2 weeks to 100 mg once-daily in reducing systolic and diastolic blood pressure at 8 weeks.” The following exposition uses the sponsor’s analyses and displays of the results of the studies. A separate statistical review by Dr. James Hung provides independent analyses of the SAS datasets submitted, and verifies the sponsor’s numbers.

A. The CANDLE Study

This was a randomized, parallel 8 week study of Candesartan versus losartan in 232 adult hypertensive patients. The design of the study was:



BL=Baseline Week DBW=Double Blind Week

* Screen/Baseline Week 0 visit allows for patients to be withdrawn from other antihypertensives prior to receiving study

** Double Blind Week 0 = Qualifying/Randomization Visit (Baseline Week 4 or optional Baseline

332 male or female patients, age 18-80 years, with essential hypertension i.e. Sitting diastolic blood pressure (Sitting DBP) of 95 mmHg to 114 mmHg on two visits were randomized to 16 mg of Candesartan or losartan 50 mg once-daily. Patients with orthostatic hypotension, history of MI or stroke within 6 months, liver or renal disease were excluded. If after 4 weeks of therapy the Sitting DBP was 90 mmHg or more, the patient was up-titrated in their assigned group to 32 mg of Candesartan or 100 mg of losartan once-daily.

The primary question was whether a difference in antihypertensive efficacy between treatments could be detected by comparing the difference in trough Sitting DBP from baseline through 8 weeks for each group. Secondary prespecified endpoints were change from baseline through week 8 of the double blind period for trough Sitting systolic blood pressure (SSBP), standing DBP, standing SBP, and like analyses of peak BP. The ITT analysis was primary, and per protocol analyses were to be done secondarily.

The losartan was obtained commercially and encapsulated for blinding to a placebo capsule. Candesartan was provided as a tablet or matching placebo. Each patient was given one active drug and on placebo. There was no all-placebo arm. The encapsulated losartan was considered equivalent to commercial losartan by virtue of dissolution testing.

The schedule of procedures was:

Study Procedures by Visit

PROCEDURE	Screening	Placebo Run-In					Double-blind				Follow-up
		Week					Week				Week
	-1	0 ^a	1	2	3	4(5)/0 ^a	2	4	6	8 or D/C	2
Informed Consent	X										
Medical History	X										
Chest X-ray					X ^c						
12-lead ECG					X					X	
Complete Physical Exam	X									X	
Brief Physical Exam		X	X	X	X	X	X	X	X		X
Trough BP Measurements	X	X	X	X	X	X	X	X	X	X	X
Peak BP Measurements					X ^b					X	
Heart Rate Measurements	X	X	X	X	X	X	X	X	X	X	X
Laboratory Assessments	X					X				X	
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	
Drug Accountability		X	X	X	X	X	X	X	X	X	
AE Assessment		X	X	X	X	X	X	X	X	X	X

- ^a If subject does not need washout of antihypertensive medications, Screening Week -1 and Placebo Run-In Week 0 can be combined into one visit. In this case, a complete physical exam should be performed
- ^b Peak blood pressure should be measured at the Placebo Run-in Week 3 visit only when the trough blood pressure measurement at that visit qualifies. If the trough blood pressure measurement does not qualify at Week 3 then wait to measure the peak blood pressure at the Placebo Run-in Week 4 visit.
- ^c Chest X-ray (PA view) performed within 3 months prior to admission into the study is an acceptable alternative.

460 patients were screened for the study. 332 were randomized to either Candesartan (n=162) or losartan (n=170). 309 patients completed the 8 week double-blind portion of the study (Candesartan n=155, losartan n=154).

Treatment compliance was measured by determining the number of capsules and tablets returned to the study coordinator from the treatment packs dispensed. Mean compliance during the 8 week double-blind study was calculated at 100.9% and 100.3% for Candesartan and losartan respectively.

The sample size of 165 patients per group was estimated to be adequate to provide 95% power to detect a true difference in mean change from baseline in trough Sitting DBP of

3 mmHg. Assuming a standard deviation of 7.5 mmHg, statistical significance on a two-tailed test with an $\alpha=0.05$ could be determined. Trough was defined as 24 ± 3 hours post dosing. Peak was defined as 6.5 ± 2.5 hours post-dosing.

Baseline characteristics of those randomized was:

**Summary of Overall Patient Baseline Characteristics by Treatment
(AM175 All Randomized Patients)**

			Candesartan Cilexetil	Losartan	Overall
Age (yrs)	Overall	N	162	170	332
		Mean	53.9	56.7	55.3
		SD	11.0	10.1	10.6
Weight (lbs)	Overall	N	161	169	330
		Mean	193.7	199.0	196.4
		SD	42.5	42.5	42.5
	Male	N	91	99	190
		Mean	206.6	213.2	210.1
		SD	35.4	38.7	37.2
	Female	N	70	70	140
		Mean	176.9	178.8	177.9
		SD	45.2	39.7	42.4
Duration of Hypertension (yrs)	Overall	N	162	169	331
		Mean	11.3	11.0	11.1
		SD	9.7	9.5	9.6
Sex	Male	N(%)	92(56.8%)	99(58.2%)	191(57.5%)
	Female	N(%)	70(43.2%)	71(41.8%)	141(42.5%)
Race	Non-Black	N(%)	144(88.9%)	147(86.5%)	291(87.7%)
	Black	N(%)	18(11.1%)	23(13.5%)	41(12.3%)
Baseline Trough Sitting DBP (mm Hg)		Mean	100.3	100.5	100.4
Baseline Trough Sitting SBP (mm Hg)		Mean	152.9	154.1	153.5

Complete tables for baseline characteristics can be found in the 10.1.2. series of tables. Baseline trough sitting blood pressure data can be found in Tables 10.2.1.01. and 10.2.1.04.; the population used for this data is ITT/LOCF. Listings by center are presented in the Appendix 12.1.8.1. series and complete listings in the Appendix 12.2.1.2. and 12.2.2.1. series.

Efficacy Results

The change from baseline in DBP and SBP, trough and peak, Sitting and standing were provided as follows:

Least Squares Means and P-Values for Treatment Group Comparisons Based on Reductions from Baseline to Double-blind Week 8 (mm Hg) in Blood Pressure Measurements (AM175 ITT/LOCF Population for Trough, ITT Population for Peak)

Parameter	Candesartan cilexetil	Losartan	p-value for comparison
Trough Sitting DBP	-11.0	-8.9	0.0158
Trough Sitting SBP	-11.9	-10.0	0.2480
Peak Sitting DBP	-12.6	-9.6	0.0054
Peak Sitting SBP	-16.5	-14.4	0.2390
Trough Standing DBP	-9.3	-7.9	0.1520
Trough Standing SBP	-10.5	-9.4	0.5092
Peak Standing DBP	-11.5	-9.4	0.0381
Peak Standing SBP	-15.2	-13.7	0.3773

Subgroup analyses of the primary endpoint results were:

Least Squares Means for Reductions from Baseline in Trough Sitting Diastolic Blood Pressure (mm Hg) by Treatment and Subpopulation (ITT/LOCF Population)

Population	Candesartan cilexetil (N)	Losartan (N)
Overall	-11.0(160)	-8.9(169)
Black	-7.8(18)	-8.9(22)
Nonblack	-11.8(142)	-9.3(147)
Age≥65 years	-11.1(25)	-11.7(35)
Age< 65 years	-10.7(135)	-8.3(134)
Female	-10.3(70)	-10.2(70)
Male	-11.3(90)	-7.8(99)

From Tables 12.1.8.3.03., 12.1.8.3.04., 12.1.8.4.01., 12.1.8.4.02., 12.1.8.4.05., and 12.1.8.4.06.

The primary endpoint of change in trough Sitting DBP from baseline through week 8 of the double-blind period for each treatment was displayed in two-week increments as below:

**Trough Sitting Diastolic Blood Pressure (mm Hg) by Treatment and Visit
(AM175 ITT/LOCF Population)**

Treatment		Baseline	DB Wk 2	DB Wk 4	DB Wk 6	DB Wk 8	DB Wk 8 (LOCF)
Candesartan cilexetil	N	160	160	157	157	155	160
	Mean	100.3	91.5	90.8	88.0	89.2	89.3
	SD	4.2	8.4	8.4	8.0	8.1	8.0
Losartan	N	169	168	165	161	157	169
	Mean	100.5	93.5	92.0	90.0	90.9	91.5
	SD	4.1	9.0	8.9	8.5	8.5	9.3

At 2 weeks the Sitting DBP change from baseline for Candesartan was 8.8 mmHg. From 2 weeks through 8 weeks the change was 2.3 mmHg. For losartan those results were 7 mmHg and 2.6 mmHg. Clearly the major antihypertensive effect occurred in the first two weeks, before any patient was uptitrated.

From baseline through week 2 patients were on either Candesartan 16 mg or losartan 50 mg once-daily. Those not responding (Sitting DBP<90 mmHg) were uptitrated. Results for those uptitrated and those not-uptitrated were:

**Trough Sitting Diastolic Blood Pressure (mm Hg) by Treatment and Visit
(AM175 ITT/LOCF Population)**

Treatment		Baseline	DB Wk 2	DB Wk 4	DB Wk 6	DB Wk 8	DB Wk 8 (LOCF)
Not Up-titrated							
Candesartan cilexetil 16 mg	N	75	75	72	73	71	75
	Mean	98.4	87.0	83.9	84.1	85.6	85.8
	SD	2.5	6.9	5.4	6.7	7.0	7.0
Losartan 50 mg	N	74	73	70	66	64	74
	Mean	99.1	89.7	84.2	84.4	86.2	87.8
	SD	3.3	9.2	6.4	6.2	6.4	9.0
Up-titrated							
Candesartan cilexetil 16, 32 mg	N	85	85	85	84	84	85
	Mean	102.1	95.5	96.8	91.5	92.3	92.4
	SD	4.7	7.6	5.3	7.6	7.7	7.7
Losartan 50, 100 mg	N	95	95	95	95	93	95
	Mean	101.6	96.4	97.7	93.8	94.2	94.4
	SD	4.4	7.8	5.5	7.7	8.3	8.4

Approximately 54% of the Candesartan patients and 58% of the losartan patients were uptitrated.

For the not-uptitrated group, the Sitting DBP change from baseline at 2 weeks for the Candesartan group was 11.4 mmHg, and 1.2 mmHg from 2 weeks through 8 weeks (LOCF). Those results for the losartan patients were 9.4 and 1.9 mmHg.

For the up-titrated group, the Candesartan result at 2 weeks was 6.6 mmHg, and for 2 through 8 weeks (LOCF) 3.1 mmHg. For losartan the results were 5.2 and 2.0 mmHg.

Safety Results

No deaths occurred in this study.

Patients who withdrew for adverse events were detailed as follows:

Adverse Events Occurring After Randomization in Patients Who Withdrew Due To an Adverse Event

Patient	Treatment and Dose	Adverse Event (Included Term)	Days on Treatment
005/001	Candesartan cilexetil 16 mg	Herpes zoster	8
008/005	Candesartan cilexetil 16 mg	Angina pectoris aggravated Myocardial infarction	2 2
004/008	Losartan 50 mg	Abdominal pain Bloating Diarrhea Fatigue Flatulence Sleep difficulty Tendinitis	0 0 0 0 0 0 0
004/016	Losartan 50 mg	Joint pain	21
005/007	Losartan 100 mg	Double vision	36
015/011	Losartan 50 mg	Headache Blood pressure increased	40 43
034/005	Losartan 50 mg	Pyelonephritis	49
036/012	Losartan 50 mg	Tachycardia supraventricular	10

Other serious adverse events were:

Serious Adverse Events in Randomized Patients

Patient	Treatment Group	Dose	Preferred Term	Days on Treatment
008/005	Candesartan cilexetil	16 mg	Myocardial Infarction	2
010/012	Losartan	100 mg	Squamous Cell Carcinoma	42
019/011	Losartan	100 mg	Dyspnea	56
034/005	Losartan	50 mg 50 mg	Ketosis Pyelonephritis	26 49
036/012	Losartan	50 mg	Tachycardia Supraventricular	10
039/023	Losartan	50 mg	Cardiac Failure	63
040/003	Losartan	50 mg	GI Hemorrhage	39
040/016	Losartan	50 mg	Adenocarcinoma	1

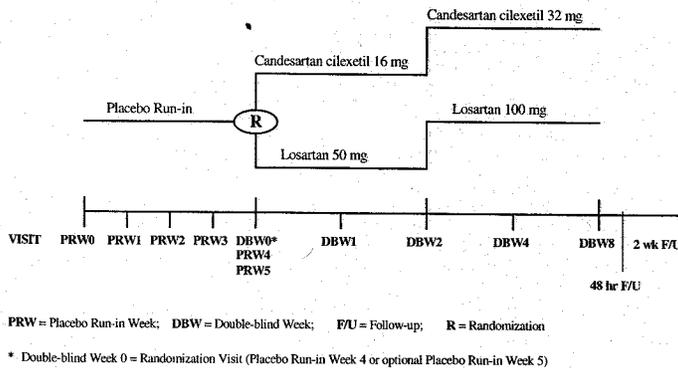
The CANDLE study will be discussed with the CLAIM studies.

B. The CLAIM Studies (Studies 230 and 231)

Studies 230 and 231 were randomized studies comparing Candesartan to losartan for antihypertensive efficacy. Each was given at the recommended starting dose (16 mg and 50 mg respectively) once-daily for 2 weeks and force-titrated to the maximum recommended dose (32 mg and 100 mg respectively) for an additional 6 weeks. The sponsor had performed other comparative studies at these doses, e.g. the CANDLE study, but with up-titration only of inadequately responding patients. Considerable discussion of the CANDLE study and new protocols ensued. During those discussions, it was noted that selection of the “usual starting dose” was somewhat arbitrary. Studies comparing the top labeled doses of Candesartan and losartan were recommended.

Additionally it was noted that losartan and Candesartan could be given twice daily, and the once-daily proposal would not test Candesartan against a BID losartan dosing regimen that provide more antihypertensive effect at the same daily dose. Finally, since the losartan used in these studies was encapsulated to maintain blinding, the sponsor needed to perform a bioequivalence study comparing the PK of the encapsulated to the nonencapsulated losartan. That has been included and the results of the PK study will be reviewed by the Biopharmaceutics reviewer.

The sponsor chose to perform studies 230 and 231 with the following design:



In study 230, 611 adult patients with Sitting DBP between 95 and 114 mm Hg were randomized. The baseline characteristics of these patients were:

			Candesartan Cilexetil	Losartan	Overall
Age (yrs.)		N	307	304	611
		Mean	55.5	55.1	55.3
		SD	9.9	11.0	10.5
Weight (lbs)	Overall	N	306	304	610
		Mean	204.7	200.6	202.6
		SD	44.5	41.3	43.0
	Male	N	178	179	357
		Mean	219.4	212.2	215.8
		SD	41.3	39.1	40.3
	Female	N	128	125	253
		Mean	184.2	184.0	184.1
		SD	40.6	38.8	39.6
Duration of Hypertension (yrs.)		N	307	304	611
		Mean	10.5	10.3	10.4
		SD	9.4	9.8	9.6
Sex	Male	N(%)	179 (58.3)	179 (58.9)	358 (58.6)
	Female	N(%)	128 (41.7)	125 (41.1)	253 (41.4)
Race	Non-Black	N(%)	245 (79.8)	245 (80.6)	490 (80.2)
	Black	N(%)	62 (20.2)	59 (19.4)	121 (19.8)
Baseline Trough Sitting DBP (mm Hg)		Mean	100.4	100.2	100.3
Baseline Trough Sitting SBP (mm Hg)		Mean	153.6	152.2	152.9

The disposition of these patients was as follows:

	Candesartan Cilexetil	Losartan	Overall
Patients Entered			926
Randomized to Double- blind (Safety population)	307	304	611
Discontinued	37 (12.1%)	37 (12.2%)	74 (12.1%)
--Lost to Follow-up	5 (1.6%)	4 (1.3%)	9 (1.5%)
--Lack of Response	8 (2.6%)	13 (4.3%)	21 (3.4%)
--Adverse Event	9 (2.9%)	6 (2.0%)	15 (2.4%)
--Consent Withdrawn	10 (3.3%)	8 (2.6%)	18 (2.9%)
--Sponsor/Investigator Decision	5 (1.6%)	6 (2.0%)	11 (1.8%)
Completed Study	268 (87.3%)	267 (87.8%)	535 (87.6%)

Complete table can be found in Table 14.1.1.01. Listing of patients can be found in Appendix 16.2.1.01. Please note that 2 additional patients in the candesartan cilexetil group discontinued due to an adverse event while in the follow-up portion of the study and therefore not during the double blind treatment period. These discontinuations are considered lost to follow-up.

The primary endpoint was the change from baseline to week 8 for trough Sitting DBP. The primary analysis was to be the ITT/LOCF population, and these results data were:

Treatment		Baseline	DB Wk 1	DB Wk 2	DB Wk 4	DB Wk 8	DB Wk 8 (LOCF)	48Hr FU	Wk 2 FU
Candesartan cilexetil	N	307	304	300	292	284	306	246	269
	Mean	100.4	93.1	91.4	89.5	89.8	90.2	91.0	89.5
	SD	4.3	8.7	8.6	9.0	9.4	9.7	9.4	9.0
Losartan	N	303	302	297	292	280	303	247	271
	Mean	100.2	93.2	92.5	90.4	90.9	91.5	93.1	89.9
	SD	4.3	8.1	8.3	8.6	8.9	9.3	8.7	9.0

Statistical analysis of the primary endpoint as well as peak results and SBP results was:

Parameter	Candesartan cilexetil	Losartan	p-value for comparison
Trough Sitting DBP*	-10.5	-9.1	0.0411
Trough Sitting SBP	-13.4	-10.1	0.0050
Peak Sitting DBP**	-12.9	-9.5	<0.0001
Peak Sitting SBP**	-15.5	-12.0	0.0032

Trough Sitting SBP results showed a similar early (i.e. by two weeks at the lower starting doses) antihypertensive effect as that noted for Sitting DBP.

Subgroup analyses were presented in the following chart:

Population	Candesartan Cilexetil			Losartan		
	N	Change from Baseline DBP	Change from Baseline SBP	N	Change from Baseline DBP	Change from Baseline SBP
Overall	284	-10.4	-13.7	280	-9.0	-10.6
Black	57	-6.4	-8.1	52	-7.7	-8.4
Nonblack	227	-11.4	-15.2	228	-9.3	-11.2
Age ≥ 65 years	58	-8.7	-12.0	50	-8.7	-9.5
Age < 65 years	226	-10.9	-14.2	230	-9.1	-10.9
Female	118	-11.1	-15.4	121	-9.8	-12.9
Male	166	-9.9	-12.5	159	-8.4	-9.0

No deaths occurred in the study. 9 patients on Candesartan and 6 on losartan withdrew due to an adverse event, however only 4 events were considered serious; 2 in the Candesartan group and 2 in the losartan arm. These events were: paroxysmal supraventricular tachycardia, cerebrovascular disorder, AF and asthma respectively.

In study 231, 654 adult patients with Sitting DBP between 95 and 114 mm Hg were randomized as in study 230.

The demographic features of these patients were:

			Candesartan Cilexetil	Losartan	Overall
Age (yrs)		N	332	322	654
		Mean	54.2	54.1	54.1
		SD	11.1	10.4	10.8
Weight (lbs)	Overall	N	329	322	651
		Mean	205.6	202.6	204.2
		SD	46.6	42.1	44.4
	Male	N	190	188	378
		Mean	219.5	213.3	216.4
		SD	44.2	38.6	41.6
Female	N	139	134	273	
	Mean	186.7	187.6	187.1	
	SD	43.3	42.3	42.7	
Duration of Hypertension (yrs)		N	332	322	654
		Mean	10.4	10.0	10.2
		SD	8.9	9.0	9.0
Sex	Male	N(%)	192 (57.8)	188 (58.4)	380 (58.1)
	Female	N(%)	140 (42.2)	134 (41.6)	274 (41.9)
Race	Non-Black	N(%)	273 (82.2)	268 (83.2)	541 (82.7)
	Black	N(%)	59 (17.8)	54 (16.8)	113 (17.3)
Baseline Trough Sitting DBP (mm Hg)		Mean	100.1	99.9	100.0
Baseline Trough Sitting SBP (mm Hg)		Mean	152.6	152.0	152.3

Disposition of these patients was:

	Candesartan Cilexetil	Losartan	Overall
Patients Entered			921
Randomized to Double-blind	332	322	654
Discontinued	15 (4.5%)	20 (6.2%)	35 (5.4%)
--Lost to Follow-up	2 (0.6%)	3 (0.9%)	5 (0.8%)
--Lack of Response	2 (0.6%)	5 (1.6%)	7 (1.1%)
--Adverse Event	6 (1.8%)	5 (1.6%)	11 (1.7%)
--Consent Withdrawn	2 (0.6%)	3 (0.9%)	5 (0.8%)
--Sponsor/Investigator Decision	3 (0.9%)	4 (1.2%)	7 (1.1%)
Completed Study	317 (95.5%)	302 (93.8%)	619 (94.6%)

As with study 230, the data for Sitting DBP over the course of the study was:

Treatment		Baseline	DB Wk 1	DB Wk 2	DB Wk 4	DB Wk 8	DB Wk 8 (LOCF)	48Hr FU	Wk 2 FU
Candesartan cilixetil	N	332	332	330	328	321	332	298	318
	Mean	100.1	92.5	91.7	89.0	89.1	89.2	90.6	88.6
	SD	3.9	7.0	7.5	8.0	8.5	8.9	8.7	8.3
Losartan	N	322	319	319	317	306	322	280	308
	Mean	99.9	93.3	93.0	90.3	90.7	91.2	93.9	88.5
	SD	4.2	8.1	7.8	8.7	8.7	9.2	8.1	9.0

Statistical analyses of change from baseline to week 8 for the ITT/LOCF population for trough and peak Sitting DBP and SBP were:

Parameter	Candesartan cilixetil	Losartan	p-value for comparison
Trough Sitting DBP*	-10.9	-8.7	0.0005
Trough Sitting SBP	-13.3	-9.8	0.0007
Peak Sitting DBP**	-11.6	-10.1	0.0375
Peak Sitting SBP**	-15.2	-12.6	0.0170

As in study 230, trough Sitting SBP change from baseline was maximal by 2 weeks for both treatments.

Subgroup analyses were presented as follows:

Population	Candesartan Cilixetil			Losartan		
	N	Change from Baseline DBP	Change from Baseline SBP	N	Change from Baseline DBP	Change from Baseline SBP
Overall	321	-11.0	-13.7	306	-8.9	-10.2
Black	57	-8.2	-7.7	47	-6.6	-5.4
Nonblack	264	-11.6	-15.0	259	-9.4	-11.0
Age ≥ 65 years	52	-11.1	-13.1	47	-8.1	-9.0
Age < 65 years	269	-11.0	-13.9	259	-9.1	-10.4
Female	137	-11.3	-15.0	127	-9.9	-12.2
Male	184	-10.9	-12.8	179	-8.3	-8.7

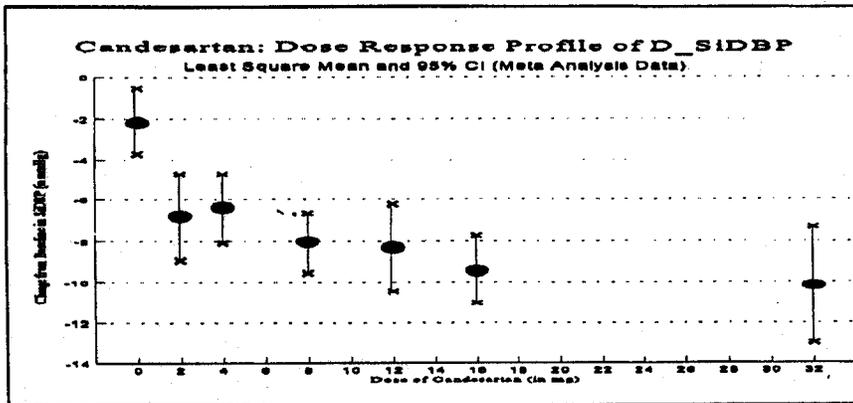
Concerning safety no deaths occurred. There were 4 serious adverse events reported; 3 in the Candesartan group (cardiac failure, myocardial infarction and accident and/or injury), and 1 in the losartan group (colitis). 11 patients withdrew for adverse reactions; 6 in the Candesartan group and 5 in the losartan arm.

Discussion

Since these comparative studies involve comparisons of specific doses, some background from the original Candesartan NDA may be helpful.

In the review of that NDA, the FDA statistician, Dr. Kooros Mahjoob, did a meta-analysis of all parallel dose response, placebo controlled studies. The NDA review can be consulted for details, but 2367 patients from 9 studies were included in the analysis. Placebo (n=630), CC (Candesartan) 2mg (n=133), CC 4 mg (n=352), CC 8 mg (n=695), CC 12 mg (n=154), CC 16 mg (347) and CC 32 mg (n=54) were included. Various analyses were done including raw means comparisons of DBP and SBP as well E-max models. The least square means result for Sitting DBP was:

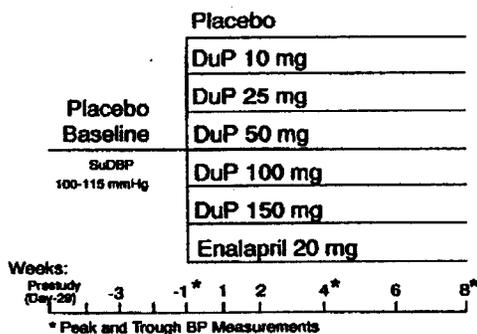
**Candesartan: Least Square Means Profile of Change From Baseline in SiDBP
All Studies in the Meta Analysis Data**



The circles are the Least Square means of the meta analysis data (all studies combined). The ANCOVA model used to calculate the Least Square Means contained the class variables and covariates (which were statistically significant in the model): Study, Dose, Sex and Race as class variables and the baseline SiDBP as the covariate.

The curves using other models and the raw means for both DBP and SBP were similar. The reviewers concluded that the CC dose response appeared to be maximal at 16 mg. Too few patients had been studied at 32 mg to rule out some additional antihypertensive effect at that dose.

In the original NDA 20386 for losartan, the medical officer, Dr. Charles Ganley, reviewed the major efficacy study (study 011) that explored a once-daily dose range from 10 mg to 150 mg with both placebo and enalapril 20 mg control arms. The design of the study was as follows:



DuP was losartan.

The results were displayed in the review:

Table 11.4. Mean Change in Trough Supine Diastolic Blood Pressure at Week 8. (All-Patients-Treated Approach)

Treatment	N	Baseline		Treatment		Change		Adj Mean	Comparison						
		Mean	S.D.	Mean	S.D.	Mean	S.D.		VS. B	VS. C	VS. D	VS. E	VS. F	VS. G	
Placebo (A)	78	103.3	3.8	97.8	8.8	-5.6	7.8	-5.3	*	NS	**	**	**	**	
LOS 10 (B)	80	104.3	3.9	96.3	9.7	-7.9	7.6	-7.8	--	NS	*	NS	NS	**	
LOS 25 (C)	82	103.3	3.7	96.5	9.5	-6.8	7.9	-6.4	--	--	**	**	**	**	
LOS 50 (D)	78	104.1	3.7	94	8.5	-10.1	7	-10.1	--	--	--	NS	NS	NS	
LOS 100 (E)	89	104.1	4.3	94.2	8	-9.9	6.9	-9.9	--	--	--	--	NS	NS	
LOS 150 (F)	84	103.4	3.4	93.7	9.4	-9.7	8	-9.5	--	--	--	--	--	NS	
ENAL 20 (G)	82	103.1	3.8	91.9	8.2	-11.2	6.7	-10.8	--	--	--	--	--	--	

NS -- Not statistically significant; * -- Treatment difference statistically significant, p<0.05; ** -- Treatment difference statistically significant, p<0.01

While losartan 25 mg once-daily was significantly effective, 50 mg once-daily gave the maximum antihypertensive effect with no additional benefit noted for either the 100 or 150 mg losartan dose.

Study 065 was a placebo controlled, 12 week study of losartan 25 mg once-daily, 50 mg once-daily and 25 mg BID in 428 randomized patients with mild to moderate hypertension. Results were:

Table 65.4. Mean Change In Trough Sitting Diastolic Blood Pressure (mmHg) At Week 12. All-Patients-Treated Approach

Treatment	N	Baseline			Treatment			Change			Adj Mean	Comparison		
		Mean	Median	S.D.	Mean	Median	S.D.	Mean	Median	S.D.		vs. B	vs. C	vs. D
Placebo (A)	102	101.3	99.0	5.1	99.3	98.5	9.8	-2.0	-2.5	8.4	-2.1	**	**	**
Losartan 25 qd (B)	105	101.8	100.0	5.5	96.0	93.0	8.4	-5.8	-6.0	6.7	-5.9	--	NS	*
Losartan 50 qd (C)	101	102.3	100.0	6.3	96.0	95.0	9.5	-6.3	-7.0	7.4	-6.6	--	--	NS
Losartan 25 bid (D)	101	102.0	101.0	5.3	94.0	93.0	8.8	-8.0	-8.0	7.9	-8.3	--	--	--

NS -- NOT STATISTICALLY SIGNIFICANT; * = TREATMENT DIFFERENCE STATISTICALLY SIGNIFICANT, P<0.05
 ** = TREATMENT DIFFERENCE STATISTICALLY SIGNIFICANT, P<0.01

The comparison between losartan 50 mg once-daily and 25 mg BID was a secondary endpoint. The difference between the regimes was not significant, but there was a numerical difference favoring the BID regimen.

For Candesartan, no study of the drug given in divided doses was provided. The approved labeling states: "With once-daily dosing, blood pressure effect was maintained over 24 hours, with trough-to-peak ratios of blood pressure effect generally over 80%." AstraZeneca did provide a study comparing the antihypertensive effects of CC 8 and 16 mg to losartan 50 mg and placebo, each given once-daily. Results of that study per the sponsor follows:

Comparison of treatments for the change from baseline to Week 8 (LVCF) in sitting DBP (mmHg). ITT population.

Treatment Comparison	Adjusted Mean	95% CI		p-value
		Lower	Upper	
24h post dose				
cand.cil. 8 mg vs losartan	-2.3	-5.3	0.6	0.115
cand.cil. 16 mg vs losartan	-3.7	-6.7	-0.8	0.013
cand.cil. 8 mg vs placebo	-8.9	-11.8	-6.0	<0.001
cand.cil. 16 mg vs placebo	-10.3	-13.2	-7.4	<0.001
6h post dose				
cand.cil. 8 mg vs losartan	1.7	-1.3	4.7	0.265
cand.cil. 16 mg vs losartan	-1.3	-4.3	1.7	0.386
cand.cil. 8 mg vs placebo	-7.6	-10.6	-4.6	<0.001
cand.cil. 16 mg vs placebo	-10.6	-13.7	-7.6	<0.001

It would appear from the chart above that the 50 mg once-daily dose of losartan is less effective than 16 mg of Candesartan, but not distinguishable from 8 mg of Candesartan.

The currently approved Candesartan labeling for **Dosage and Administration** states: "Dosage must be individualized. Blood pressure response is dose related over the range of 2 to 32 mg. The usual starting dose of ATACAND is 16 mg once-daily when it is used as monotherapy in patients who are not volume depleted. Atacand can be administered once or twice daily with total daily doses ranging from 8 mg to 32 mg. Larger doses do not appear to have a greater effect, and there is relatively little experience with such doses. Most of the antihypertensive effect is present within 2 weeks, and maximal blood pressure reduction is generally obtained within 4 to 6 weeks of treatment with ATACAND."

For losartan that section states:

"The usual starting dose of COZAAR is 50 mg once-daily, with 25 mg used in patients with possible depletion of intravascular volume (e.g. patients treated with diuretics) (see WARNINGS, hypotension-Volume Depleted Patients) and patients with hepatic impairment (see PRECAUTIONS, General). COZAAR can be administered once or twice daily with total daily doses ranging from 25 mg to 100 mg.

If the antihypertensive effect measured at trough using once-a-day dosing is inadequate, a twice-a-day or an increase in dose may give a more satisfactory response."

In the CANDLE study, treatment was initiated at 16 mg of CC and 50 mg of losartan once-daily for 2 weeks, followed by an elective titration to 32 mg or 100 mg once-daily respectively. In the CLAIM studies, treatment was initiated at 16 mg and 50 mg once-daily for CC and losartan respectively with a forced titration at 2 weeks to 32 mg of CC and 100 mg of losartan once-daily.

The following chart details the change in trough Sitting DBP from baseline to week 2 and then from week 2 through week 8 (LOCF) for each treatment in each study.

STUDY 230

	Baseline to week 2 siDBP	Week 2 to week 8 siDBP
Candesartan	-9 mm Hg	-1.2 mm Hg
Losartan	-7.7 mm Hg	-1.0 mm Hg

STUDY 231

	Baseline to week 2 siDBP	Week 2 to week 8 siDBP
Candesartan	-8.4 mm Hg	-2.5 mm Hg
Losartan	-6.9 mm Hg	-1.8 mm Hg

The sponsor observed that the week 2 to week 8 changes were greatest in those not responding to the initial dose, and provided the following subgroup results for study 230 and 231.

Study 230:

Change from Week 2 to Week 8 in Trough Sitting Diastolic and Systolic Blood Pressure ITT Population)

	Parameter	Candesartan cilexetil 16 mg to 32 mg	Losartan 50 mg to 100 mg
DBP < 90 at Week 2	N	126	104
	Trough Sitting DBP	1.5	1.9
SBP < 140 at Week 2	N	133	137
	Trough Sitting SBP	1.6	3.3
DBP ≥ 90 at Week 2	N	158	176
	Trough Sitting DBP	-3.5	-3.0
SBP ≥ 140 at Week 2	N	151	143
	Trough Sitting SBP	-3.6	-4.9

Study 231:

	Parameter	Candesartan cilexetil 16 mg to 32 mg	Losartan 50 mg to 100 mg
DBP < 90 at Week 2	N	134	112
	Trough Sitting DBP	0.3	0.8
SBP < 140 at Week 2	N	151	135
	Trough Sitting SBP	0.4	2.4
DBP ≥ 90 at Week 2	N	187	194
	Trough Sitting DBP	-5.0	-3.7
SBP ≥ 140 at Week 2	N	170	171
	Trough Sitting SBP	-4.6	-4.1

In the CANDLE study where elective titration after 2 weeks was permitted, approximately 54% of the Candesartan patients and 58% of the losartan patients were up-titrated.

For the not up-titrated group, the trough Sitting DBP change from baseline at 2 weeks for the Candesartan group was 11.4 mmHg, and 1.2 mmHg from 2 weeks through 8 weeks (LOCF). Those results for the losartan patients were 9.4 and 1.9 mmHg.

For the up-titrated group, the Candesartan result at 2 weeks was 6.6 mmHg, and for 2 through 8 weeks (LOCF) 3.1 mmHg. For losartan the results were 5.2 and 2.0 mmHg.

**Trough Sitting Diastolic Blood Pressure (mm Hg) by Treatment and Visit
(AM175 ITT/LOCF Population)**

Treatment		Baseline	DB Wk 2	DB Wk 4	DB Wk 6	DB Wk 8	DB Wk 8 (LOCF)
Not Up-titrated							
Candesartan cilexetil 16 mg	N	75	75	72	73	71	75
	Mean	98.4	87.0	83.9	84.1	85.6	85.8
	SD	2.5	6.9	5.4	6.7	7.0	7.0
Losartan 50 mg	N	74	73	70	66	64	74
	Mean	99.1	89.7	84.2	84.4	86.2	87.8
	SD	3.3	9.2	6.4	6.2	6.4	9.0
Up-titrated							
Candesartan cilexetil 16, 32 mg	N	85	85	85	84	84	85
	Mean	102.1	95.5	96.8	91.5	92.3	92.4
	SD	4.7	7.6	5.3	7.6	7.7	7.7
Losartan 50, 100 mg	N	95	95	95	95	93	95
	Mean	101.6	96.4	97.7	93.8	94.2	94.4
	SD	4.4	7.8	5.5	7.7	8.3	8.4

Since there were no Candesartan 16 mg and losartan 50 mg arms, it is not possible to conclude that the decrease in blood pressure from week 2 to week 8 seen in “nonresponders” compared to “responders” was due to the higher dose of each drug, rather than a slower response at the lower doses (or placebo, had that been included). Without Candesartan 16 mg and losartan 50 mg treatments continued for eight weeks, it is not possible to conclude that the higher doses were necessary to reach the blood pressures found at 8 weeks. The results do not support the conclusion that the significant differences found were due to the top labeled doses, rather than the starting doses.

The results of the CLAIM studies as well as the CANDLE study do support the conclusion that 16 mg CC once-daily provides more antihypertensive effect than losartan 50 mg given once-daily. Higher doses did not provide more antihypertensive effect than the usual starting doses in the ITT analyses. That finding is consistent with the data from the original NDAs. Suggestions that the 32 mg dose once-daily of Candesartan might be superior to 100 mg of losartan once-daily in patients not adequately responding to the usual starting doses would need to be studied in a properly designed trial. Since the CANDLE study demonstrated that once-daily 16 mg of Candesartan and 50 mg of losartan provided similar percentages of adequately controlled patients after 2 weeks (46% and 42% respectively), the clinical superiority of one drug over the other was not evident.

Moreover, the twice daily losartan regimen as well as the low end of the approved dose ranges of both drugs have not been evaluated. These studies, therefore, do not support the superiority of one drug versus the other. However, evidence of one point to point specific regimen superiority of Candesartan to losartan is provided, and on the basis of these studies AstraZeneca requests that the following information be added to the **Clinical Trials** section of the labeling:

“Two identically designed, concurrently conducted, 8 week, multicenter, double-blind, randomized, forced-titration studies were performed to compare the antihypertensive efficacy of candesartan cilexetil and losartan at their once-daily maximum doses. Candesartan cilexetil initiated at 16 mg once-daily and force-titrated at 2 weeks to 32 mg once-daily was statistically significantly more effective than losartan 50 mg once-daily forced-titrated at 2 weeks to 100 mg once-daily in reducing systolic and diastolic blood pressure at 8 weeks. In these studies, both agents were well-tolerated.” This statement is literally true, and supported by two adequate and well-controlled studies. My concern is that overall drug clinical superiority may be inferred from the statement. If comparative effectiveness information were to be provided in the label, the average sitting DBP and sitting SBP differences should be provided so the clinician has some idea of the magnitude of difference found. While it is not generally the responsibility of one manufacturer to provide full information about another manufacturer’s competing drug, when a comparative effectiveness claim is made balanced information should be provided. Suggestions for such are:

1. Given the approved dose ranges and regimens for Candesartan and losartan, no data are available to suggest that patients with hypertension would be more satisfactorily treated with one drug or the other.
2. Losartan may provide more antihypertensive effect by giving the 50 mg usual starting dose BID, rather than QD. That regimen was not studied in the comparative studies provided. No data comparing BID and QD regimens of Candesartan have been provided.
3. In these studies, the antihypertensive effects of both Candesartan and losartan occurred in the first 2 weeks of therapy on 16 mg and 50 mg once-daily respectively. Up-titrating to 32 mg and 100 mg once-daily respectively did not provide additional benefit.

HEPATICALLY IMPAIRED PATIENTS

The sponsor included study SH-AHC-0009, Pharmacokinetics of Candesartan Cilexetil in Patients with Moderate to Severe Impairment of Liver Function in this submission.

The original NDA contained study EC023 that evaluated the PK of Candesartan at 12 mg once-daily for 7 days in 25 subjects with and without impaired hepatic function. Impaired hepatic function was categorized as mild to moderate liver disease with fatty liver, hepatitis patients but not cirrhotics considered for entrance. Liver disease was determined by liver enzyme, antipyrine clearance, sonogram or biopsy. 13 hepatically impaired patients were entered, 1 withdrew. 12 normal subjects entered.

The PK results for day 1 were:

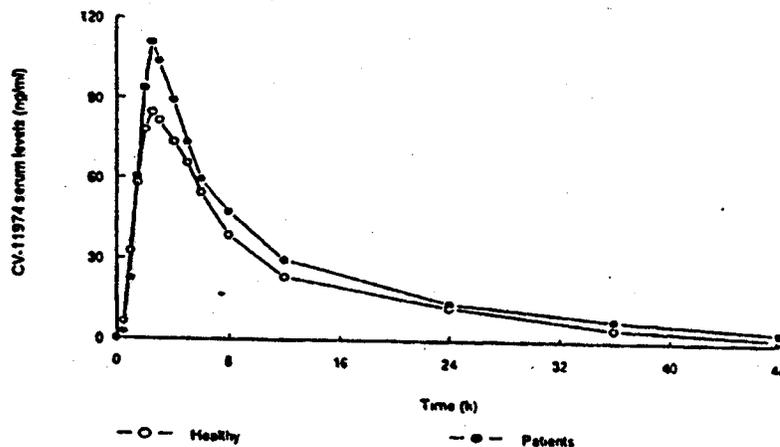
	Arithmetic					Geometric		
	Mean	SD	95% C.I. of the mean lower - upper	Median	75% percentile	Mean	SD	95% C.I. of the mean lower - upper
$T_{1/2}$ (h)	12	5.3	8.4 - 15	10.5	14	109	40.1	87.1 - 137
C_{max} (ng/ml)								
T_{max} (h)	2.7	0.55	2.3-3.0	2.5	3.0	881	234	698 - 1112
AUC _{0-∞} (ng·h/ml)						1030	483	776 - 1367
AUC _{0-t} (ng·h/ml)*						1107	560	818 - 1495
AUC _{0-∞} (ng·h/ml)						11	3.2	9.0 - 13
MRT _{0-∞} (h)								

* 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	8.4	11	95.2	29.9	78.4 - 116
C_{max} (ng/ml)								
T_{max} (h)	3.0	1.4	2.2 - 3.9	2.5	3.2	706	314	541 - 927
AUC _{0-∞} (ng·h/ml)						864	288	703 - 1062
AUC _{0-t} (ng·h/ml)*						909	307	737 - 1120
AUC _{0-∞} (ng·h/ml)						11	2.7	9.3 - 12.8
MRT _{0-∞} (h)								

* t = timepoint of last measurable concentration above blq



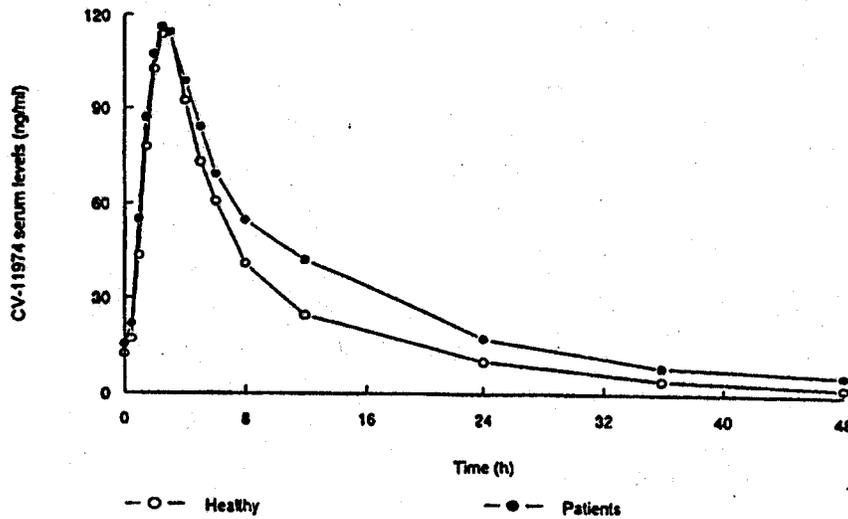
Results for day 7 were:

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	4.2	9.5 - 15	10	15			
C _{max} (ng/ml)	15.4	13.8	6.58 - 24.1	14.1	19.4	112	60.2	85.3 - 147
C _{min} (ng/ml)						45.3	18.9	35.1 - 58.4
T _{max} (h)	2.8	1.1	2.2 - 3.5	2.5	3.3			
T _{23h} (actual)								
AUC _{0-∞} (ng h/ml)						1080	458	834 - 1399
R _{ac}						1.0	0.31	0.80 - 1.2
PTF						2.1	1.0	1.6 - 2.8
PTS						7.7	12	3.7 - 16
MRT _{0-∞} (h)						12	2.6	10 - 14

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)	10	2.1	8.2 - 11	10	11			
C _{max} (ng/ml)	12.3	5.12	9.03 - 15.5	11.1	16.0	116	31.2	98.0 - 137
C _{min} (ng/ml)						36.9	8.48	32.0 - 42.6
T _{max} (h)	2.6	0.36	2.4 - 2.8	2.5	3.0			
T _{23h} (actual)								
AUC _{0-∞} (ng h/ml)						880	205	760 - 1018
R _{ac}						1.0	0.38	0.8 - 1.2
PTF						2.8	0.47	2.5 - 3.1
PTS						8.2	5.0	6.7 - 13
MRT _{0-∞} (h)						10	1.3	9.3 - 11



Unbound fraction results for days 1 and 7 were:

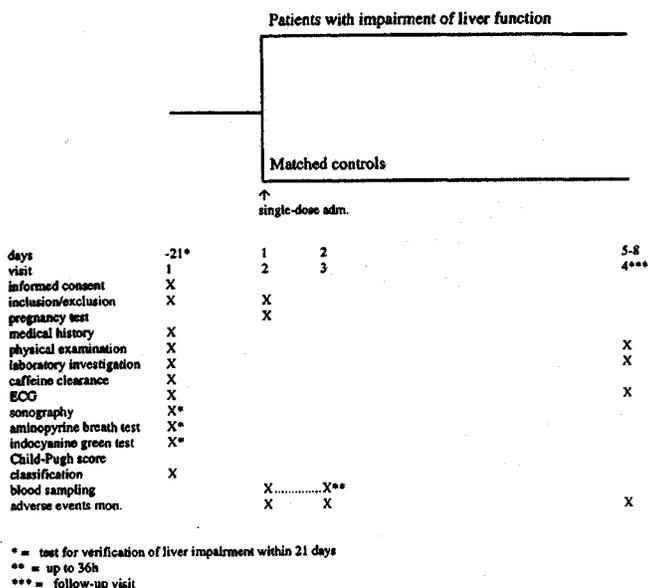
UNBOUND CV-11974 IN SERUM IN % OF TOTAL AMOUNT OF CV-11974

Healthy volunteers			Liver patients		
Subject	Day 1	Day 7	Subject	Day 1	Day 7
1	0.446	0.414	11	0.610	0.633
2	0.471	0.440	12	0.710	
3	0.468	0.454	13	0.469	0.436
4	0.494	0.436	14	0.428	0.433
5	0.481	0.479	15	0.438	0.392
6	0.466	0.468	16	0.420	0.410
7	0.550	0.550	17	0.510	0.527
8	0.501	0.544	18	0.483	0.498
9	0.555	0.521	19	0.540	0.520
10	0.543	0.556	21	0.488	0.458
20	0.463	0.509	22	0.545	0.520
25	0.520	0.494	23	0.596	0.595
			24	0.563	0.549
Mean	0.497	0.489	Mean	0.523	0.498
SD	0.037	0.048	SD	0.083	0.074
Lower limit of 95% C.I.	0.473	0.458	Lower limit of 95% C.I.	0.473	0.450
Upper limit of 95% C.I.	0.520	0.519	Upper limit of 95% C.I.	0.573	0.545
Median	0.488	0.487	Median	0.510	0.509

None of the numerical differences were statistically significant. On the basis of this study, the currently approved labeling states that “no differences in the pharmacokinetics of candesartan were observed in patients with mild to moderate chronic liver disease.”

The newly submitted study, AHC-0009, was completed in April 1997. It was a single center, open PK study of single 16 mg dose Candesartan in 12 patients with moderate to severe liver disease compared to 12 healthy volunteers matched by age, gender and weight.

The design of the study was:



Impaired liver function was determined by using the Child-Pugh methodology as shown:

Table 9.4.3:1 Child-Pugh score classification

	1 point	2 points	3 points
Albumin (g%)	>3.5	2.8-3.5	<2.8
Total Bilirubin (mg%)	<2.0	2.0-3.0	>3.0
Quick-test (PT) (%)*	>70	40-70	<40
Ascites	no	moderate	severe
Encephalopathy	no	I-II	III-IV

Child-Pugh A: 5-6 points, Child-Pugh B: 7-9 points, Child-Pugh C: 10-15. Child-Pugh C patients were not included in the study due to the severity of their disease.

* % of normal value

6 Child-Pugh A and 6 Child-Pugh B patients were entered. For analysis purposes these were all included in the primary pre-specified analysis. While not called for by the protocol, analyses of each group separately versus the matched controls were done.

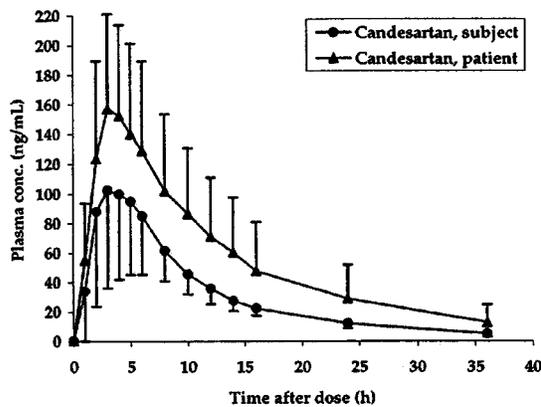
The major PK analytic results were:

Table 11.4.1:1 $AUC_{0-\infty}$ and C_{max} for candesartan after a single oral dose of candesartan cilixetil 16 mg to patients with moderate to severe impairment of liver function (n= 12) and to healthy volunteers (n=12). Medians and 95% confidence intervals are given.

Parameters	Group	Estimate	95% CI	
			Lower	Upper
$AUC_{0-\infty}$ (ng*h/ml)	Patients	2021	1490	2739
	Healthy volunteers	1135	900	1430
C_{max} (ng/ml)	Patients	156	116	208
	Healthy volunteers	95	65	138

Table 11.4.1:2 Analysis of $AUC_{0-\infty}$ (ng*h/mL). Estimate and 95% confidence interval of the ratio of true group medians.

Ratio	Estimate	95% CI	p-value
Patients/Healthy volunteers	1.78	1.14; 2.78	0.016



Subject = healthy volunteer

Subgroup analyses of Child-Pugh A and B versus control were:

Table 11.4.5:1 Candesartan after a single oral dose of candesartan cilixetil 16 mg to patients grouped according to degree of impairment of liver function (Child-Pugh A, n=6 or Child-Pugh B, n=6) and matching healthy volunteers. Medians and 95% confidence intervals are given.

Parameters	Group	Estimate	95% CI
$AUC_{0-\infty}$ (ng*h/ml)	Patients, Child-Pugh A	1730	1160; 2578
	Matched healthy volunteers	1335	869; 2051
	Patients Child-Pugh B	2361	1327; 4200
	Matched healthy volunteers	965	745; 1250
C_{max} (ng/ml)	Patients Child-Pugh A	182	122; 272
	Matched healthy volunteers	117	57; 237
	Patients Child-Pugh B	133	79; 245
	Matched healthy volunteers	77	48; 122

Concerning safety, no deaths or withdrawal for adverse events occurred. Two serious adverse events occurred in the hepatically impaired patients. One patient had an accidental injury of the shoulder, and another developed erysipelas. Both were considered unrelated to the drug.

Adverse events were reported as follows:

Patients with impaired liver function					
Run-in (n=12)	Cand. cil. (n=12)	No drug (n=12)			
Respiratory infection	2	Fatigue	2	Accident and/or injury	1
Coughing	1	Bronchitis/bronchitis aggr	1	Bronchitis/bronchitis aggr	1
Dysphonia	1	Coughing	1	Coughing	1
		Dizziness/ vertigo	1	Dizziness/vertigo	1
		Dysphonia	1	Dysphonia	1
		Respiratory infection	1	Erysipelas/erysipelas aggr	1
				Leukocytosis	1
				Respiratory infection	1
Healthy volunteers					
Run-in (n=12)	Cand. cil. (n=12)	No drug (n=12)			
		Headache	1	Dizziness/vertigo	1

The sponsor also provided a listing of postmarketing reports involving hepatic disease. There were 10 reports in 9 patients:

Case Numbers	Sex/ Age	CC ^a dose	Hepatic Disease	Other Drugs Also Suspected	Adverse Event(s)	Clinical Outcome/Comments
2000AH07603	M/73	16mg	Hepatic colic	None	Hepatic colic	Patient recovered without sequelae.
2000AH01411	M/67	8mg	Chronic Hepatitis C	Temocapril	Pancytopenia Platelet count decreased White blood cells decreased	Patient recovered without sequelae. Negative rechallenge.
2000AH01401	M/77	Unknown	Nonspecific Hepatitis	Spironolactone 25mg	Acute renal failure Condition aggravated	Acute renal failure may be related to dehydration. The patient improved and was discharged. He developed sudden cardiorespiratory arrest and died 2 weeks later when he underwent a renal scintigraphy and a captopril test.
2000AH01153	M/59	4mg (intermittently)	Chronic Hepatitis	Ethanol alcohol use	Aggravation of chronic hepatitis Abdominal discomfort Malaise Anorexia Bilirubin increased	Patient recovered with evidence of cirrhosis. Physician assessed a possible unidentified infection as the cause for the event.
2000AH01107	F/72	2mg ongoing	Chronic Hepatitis C	Paramidin 300mg warfarin	Increased PT/INR Hemoglobin decreased	Recovering/resolving

Case Numbers	Sex/ Age	CC ^a dose	Hepatic Disease	Other Drugs Also Suspected	Adverse Event(s)	Clinical Outcome/Comments
1999AU12263	F/81	Unknown ongoing	Hepatitis A	None	Constipation Nervous Insomnia Lack of appetite	No followup information available.
1999AH02398	F/77	8mg	Non-A Non-B Hepatitis	Bezafibrate Nizatidine azulene sulfonate sodium/L- glutamine allopurinol	CPK increased	Patient recovered without sequelae.
1999AH02052	F/77	4mg	Hepatitis C	Trimebutine maleate 300mg terprenone 150mg rebamipide 300 mg	SGOT increased SGPT increased Fatigability generalized	Recovering/resolving
1997AU01985	M/41	8mg	Hepatitis A	Acebutalol	Arrythmia	Patient recovered without sequelae.
1996AU02726 ^b	M/41	8mg	Hepatitis A	None	Back Pain	Patient recovered without sequelae.

^a CC = candesartan cilexetil

^b same patient as 1997AU01985 with additional AE reported

Although the hepatic events do not appear to have been caused by Candesartan, it should be noted that the dose of Candesartan (where known) was less than the recommended starting dose.

Discussion

The results of this study do suggest that, when a single oral 16 mg dose of Candesartan is given, patients with moderate hepatic impairment (Child-Pugh A and B) have increased C_{max} and AUC compared to control. It is unclear whether patients with this degree of hepatic impairment need special dosing limitations, and very severely ill patients were not studied. The sponsor has requested a labeling change to delete reference to the study EC023 and include the results of this study. They also request a Precaution be added and a change in dosing instructions to consider a lower starting dose in patients with “moderate hepatic impairment.” While adding the results of AHC-0009 to those of EC023 would be reasonable, terms such as moderate and severe may not be clear to the clinician. The specific study inclusion criteria might be provided, i.e. Child-Pugh classification. For those patients with Child-Pugh B and C hepatic impairment. The suggestion that a dose lower than 16 mg be used as the starting dose in patients with moderate and severe hepatic impairment can be included in the labeling.

OVERDOSAGE

The currently approved Candesartan label describes one overdose case, a 43 year old female who intentionally took 160 mg of Candesartan along with other drugs and recovered after gastric lavage and observation. Since the original approval, 4 additional overdose cases were reported as summarized in the following table:

Cases of Overdose with Candesartan Cilexetil

Case ID#	Sex	Age (yrs)	Candesartan cilexetil dose (mg)	Concomitant Medications (Overdosed)	Adverse Event	Clinical Outcome
1998AH00007	Female	16	432 mg	None	Suicide attempt by drug overdose	Recovery
1999AH00003	Male	35	80-128 mg	Alprazolam, Logimax	Suicide attempt by drug overdose, blood pressure low, semi-coma	Recovery
1999AU10923	Male	56	448 mg	None	Intentional overdose, tachycardia/bradycardia, hypotension	Recovery
1999AH01324	Male	41	4 mg	Unspecified	Depression	Died

The 41 year old male who died had been taking 4 mg of Candesartan and was under treatment for depression and epilepsy. The patient was suicidal and died on 7/4/99 from an overdose of medication and alcohol, but it is unknown if Candesartan was being used at all at the time of the overdose.

The 16 year old female who took 432 mg of Candesartan recovered overnight without treatment or observation. Hypotension was reported in the two other cases.

Based on these case reports the sponsor proposes to replace the description of the one overdose case currently present in the labeling with the following general information based on all available cases:

“The most likely manifestation of overdosage would be hypotension, dizziness, and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension should occur, supportive treatment should be initiated.”

The sponsor notes that these changes are consistent with the more recently approved Candesartan-Hydrochlorothiazide drug labeling. The revision retains all other approved portions of the overdose section, and the new wording is the same as has been approved for the Candesartan portion of the combination drug labeling.

CONCLUSIONS AND RECOMMENDATIONS

The CANDLE and CLAIM studies do demonstrate the Candesartan 16 mg once daily provides on average more antihypertensive effect (approximately 2 mmHG for sitting DBP) compared to 50 mg of losartan once daily. The sitting DBP measurement has been accepted as a surrogate for clinical benefit to approve new antihypertensive drugs. While a 2 mmHg difference from control would be sufficient for a demonstration of effectiveness, the translation of that difference into numbers of lives saved, strokes or myocardial infarctions prevented, which are the clinical parameters of importance, is not established. The usual comparator is placebo. Here the comparator is another active sartin. In either case the studies reconfirm that Candesartan is effective as an antihypertensive. However, they do not establish clinical superiority of Candesartan to losartan. Comparative effectiveness data of antihypertensives may be of interest to clinicians, and the Candesartan labeling can be revised to contain the results of these studies. If that is done, it should be made clear that both drugs are effective and Candesartan was not shown to be clinically superior to losartan. Clinically, either drug can be used to treat hypertension successfully, and no superior efficacy can be assumed from a 2 mmHg average difference in sitting DBP of one dose versus another. For individual antihypertensive drugs we recommend individualization of dosing, and provide a dose range to be used clinically. The same is true for comparing doses of different drugs. We do not have data on BID dosing of Candesartan and losartan, and there are data to suggest that BID losartan may give more antihypertensive effect than QD dosing.

If comparative effectiveness information were to be provided in the label, the average sitting DBP and sitting SBP differences should be provided so the clinician has some idea of the magnitude of the differences found.

Other suggested modifying language that might be included is:

1. Given the approved dose ranges and regimens for Candesartan and losartan, no data are available to suggest that patients with hypertension would be more satisfactorily treated with one drug or the other.
2. Losartan may provide more antihypertensive effect by giving the 50 mg usual starting dose BID, rather than QD. That regimen was not studied in the comparative studies provided. No data comparing BID and QD regimens of Candesartan have been provided.
3. In these studies, the antihypertensive effects of both Candesartan and losartan occurred in the first 2 weeks of therapy on 16 mg and 50 mg once-daily respectively. Up-titrating to 32 mg and 100 mg once-daily respectively did not provide additional benefit.

Concerning the other proposed labeling changes, the results of the new PK study in hepatically impaired patients can be included with information on the Child-Pugh scale. The suggested dose modification in hepatically impaired patients can be included. The revised overdose section is acceptable.

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