# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

**NDA** 20-838 SE4-015 **SUBMISSION DATE:** SEPTEMBER 27, 2001
**DRUG NAME:** Candesartan cilexetil, Atacand®
**STRENGTH AND FORMULATION:** 4 mg, 8 mg, 16 mg and 32 mg tablets
**SPONSOR:** AstraZeneca
**REVIEWER:** B. Nhi Nguyen, Pharm.D.
**TYPE OF SUBMISSION:** supplemental NDA

**BACKGROUND:** Candesartan cilexetil is a pro-drug that is completely and rapidly metabolized to the active metabolite candesartan (also known as MI or CV-11974). Candesartan is mainly eliminated unchanged in the urine and bile. To a minor extent it is eliminated hepatically to the inactive metabolite MII (also known as CV-15959). The elimination T ½ is approximately 9-10 hours in healthy volunteers and slightly longer in hypertensive patients.

Candesartan cilexetil is approved for the treatment of hypertension. For the original NDA, the sponsor conducted a study in patients with mild to moderate liver function that did not show a clinically relevant change in candesartan pharmacokinetics. AUC was 20% higher in patients with mild to moderate hepatic impairment compared to matched controls. No accumulation of candesartan was noted. The inactive metabolite, M2, was not measured.

**SUMMARY:** This supplemental NDA contains data from clinical trials, conducted under IND 47,944, that were designed to investigate the comparative efficacy between candesartan and losartan. This supplement contains three comparative efficacy studies, one bioequivalence study and one pharmacokinetic study. The purpose of the pharmacokinetic study was to compare the pharmacokinetics of candesartan in mild to moderate hepatic impairment patients (defined by Child Pugh) to normal controls. The review of the pharmacokinetic and bioequivalence studies is included in this review.

**Study SH-AHC-0015 – Bioequivalence study**
Because the comparative efficacy studies used encapsulated losartan for blinding purposes, the sponsor conducted a bioequivalence study to ensure that the encapsulation did not affect the pharmacokinetics of losartan. The pharmacokinetics of a single dose of commercially available losartan potassium 50 mg was compared to an intact commercially available losartan potassium tablet that was encapsulated in a gelatin capsule. The randomized, two-way, crossover study was conducted in 40 healthy, young subjects.

The encapsulation did not significantly affect the pharmacokinetics of commercially available losartan. The encapsulated losartan was bioequivalent to commercially available losartan. The least squares estimates and 90% confidence intervals were within 0.80-1.25 (See table).

***Table 1. Least squares estimates and 90% CI for the ratio of treatment medians (encapsulated/standard tablet) for losartan and active metabolite***

| | Losartan | | EXP 3174 | |
|---|---|---|---|---|
| | Estimate | 90% CI | Estimate | 90% CI |
| $AUC_{0-\infty}$ | 1.00 | 0.94 – 1.05 | 1.02 | 0.98 – 1.07 |
| $AUC_{0-t}$ | 0.99 | 0.93 – 1.05 | 1.02 | 0.98 – 1.07 |
| Cmax | 1.04 | 0.93 – 1.17 | 1.03 | 0.97 – 1.10 |

The table below shows the similar pharmacokinetics between commercially available losartan potassium and encapsulated losartan for both losartan and its active metabolite, EXP 3174.

***Table 2. Losartan and active metabolite pharmacokinetic parameters for both formulations***

| Parameter | Losartan | | EXP 3174 | |
|---|---|---|---|---|
| | ET | ST | ET | ST |
| $AUC_{0-\infty}$ (ng*h/mL) | 372 ± 124 | 374 ± 120 | 1952 ± 568 | 1931 ± 629 |
| $AUC_{0-t}$ (ng*h/mL) | 354 ± 125 | 358 ± 120 | 1923 ± 564 | 1903 ± 625 |
| Cmax (ng/mL) | 206 ± 108 | 204 ± 127 | 248 ± 96 | 243 ± 94 |
| Tmax (h) | 1.1 ± 0.5 | 1.1 ± 0.6 | 3.8 ± 0.6 | 4.0 ± 1.1 |
| T ½ (h) | 2.1 ± 0.6 | 2.0 ± 0.5 | 6.6 ± 0.7 | 6.3 ± 0.8 |

Mean ± SD
ET = encapsulated tablet
ST = standard tablet

**Study SH-AHC-0009 – Mild to Moderate Hepatic Impairment PK Study**

The sponsor compared the pharmacokinetics from a single dose of candesartan cilexetil 16 mg in twelve patients with mild (n=6) and moderate (n=6) hepatic impairment to healthy controls that were matched for age, gender, and weight. Hepatic impairment was defined by the Child Pugh criteria. Patients had a statistically significant increase in candesartan $AUC_{0-\infty}$ of 78 % and Cmax of 65 % compared to volunteers. (See table below.) Half-life was similar in both groups (approximately 9 hours).

***Table 3. Candesartan PK parameters of hepatic impairment patients and volunteers***

| **Parameter** | **Group** | **Estimate (95% CI)** | **Estimate (95% CI) Ratio patient:volunteer** | **p-value** |
|---|---|---|---|---|
| $AUC_{0-\infty}$ (ng*h/mL) | Patient | 2021 (1490, 2739) | 1.78 (1.14, 2.78) | 0.016* |
| | Healthy volunteer | 1135 (900, 1430) | | |
| Cmax (ng/mL) | Patient | 156 (116, 208) | 1.65 (1.04, 2.61) | 0.036* |
| | Healthy volunteer | 95 (65, 138) | | |

* statistically significant

Slight insignificant increases in the inactive metabolite $AUC_{0-t}$ and Cmax were observed in patients but not in volunteers.

Post-hoc analysis of each hepatic impairment group showed that patients with mild liver impairment had a 30% increase in candesartan $AUC_{0-\infty}$ and a 56% increase in candesartan Cmax compared to healthy volunteers. Patients with moderate liver impairment had a 145% increase in candesartan $AUC_{0-\infty}$ and a 73% increase in candesartan Cmax compared to healthy volunteers. Only the comparison between moderate hepatic impairment patients to healthy volunteers was statistically significant. (See Table below.)

***Table 4. Candesartan PK parameters of hepatic impairment patients and volunteers***

| Parameter | Group | Estimate (95% CI) | Ratio group:volunteer | p-value |
|---|---|---|---|---|
| $AUC_{0-\infty}$ (ng*h/mL) | Mild (CP A) | 1730 (1160, 2578) | 1.30 (0.70, 2.38) | 0.324 |
| | Healthy volunteer | 1335 (869, 2051) | | |
| | Moderate (CP B) | 2361 (1327, 4200) | 2.45 (1.16, 5.14) | 0.027* |
| | Healthy volunteer | 965 (745, 1250) | | |
| Cmax (ng/mL) | Mild (CP A) | 182 (122, 272) | 1.56 (0.80, 3.07) | 0.150 |
| | Healthy volunteer | 117 (57, 237) | | |
| | Moderate (CP B) | 133 (79, 245) | 1.73 (0.71, 4.24) | 0.174 |
| | Healthy volunteer | 77 (48, 122) | | |

* statistically significant
CP = Child Pugh

**RECOMMENDATION:** The Office of Clinical Pharmacology and Biopharmaceutics has completed the review of study SH-AHC-0015 and study SH-AHC-0009, and recommends the following:

1. The encapsulated losartan tablet used in clinical trials for blinding purposes is bioequivalent to the commercially available losartan tablet.

2. The Office of Clinical Pharmacology and Biopharmaceutics' agrees with most of the sponsor's proposed labeling, but also recommends the following marked labeling changes:

- **Special Populations**

*Hepatic Insufficiency:* The pharmacokinetics of candesartan were compared in patients with mild and moderate hepatic impairment to matched healthy volunteers following a single oral dose of 16 mg candesartan cilexetil. The increase in AUC for candesartan was 30% in patients with mild hepatic impairment (Child Pugh A) and 145% in patients with moderate hepatic impairment (Child Pugh B). The increase in Cmax for candesartan was 56% in patients with mild hepatic impairment and 73% in patients with moderate hepatic impairment. The pharmacokinetics after candesartan cilexetil administration have not been investigated in patients with severe hepatic impairment. No initial dosage adjustment is necessary in patients with mild hepatic impairment. In patients with moderate hepatic impairment, ATACAND should be initiated at a lower dose (see DOSAGE AND ADMINSTRATION).

- **PRECAUTIONS**

**Impaired Hepatic Function**

Based on pharmacokinetic data that demonstrate significant increases in candesartan AUC and Cmax in patients with moderate hepatic impairment, a lower initial dose should be used for

patients with moderate hepatic impairment. (see DOSAGE AND ADMINISTRATION, and CLINICAL PHARMACOLOGY, Special Populations).

- **DOSAGE AND ADMINISTRATION**

No initial dosage adjustment is necessary for elderly patients, for patients with mildly impaired renal function, or for patients with mildly impaired hepatic function (see CLINICAL PHARMACOLOGY , Special Populations ). In patients with moderate hepatic impairment, ATACAND should be initiated at 8 mg and titrated to response. (See CLINICAL PHARMACOLOGY, Special Populations).

The optional intra-division briefing was held on May 1, 2002. Patrick Marroum, Gabriel Robbie, and Krishnan Viswanadhan attended.

B. Nhi Nguyen, Pharm.D.
Division of Pharmaceutical Evaluation I

FT Initialed by Gabriel Robbie, Ph.D._____
CC list: HFD-110: NDA 20-838; HFD-860: (Nguyen, Marroum, Mehta); CDER Central Document Room

# APPENDIX I

**STUDY REPORT:** SH-AHC-0015 ITEM-VOLUME-PAGE: 006-002-019 TO 349
**TITLE:** A bioequivalence study comparing a single dose of 50 mg losartan potassium, given either as a commercial Cozaar® tablet 50 mg or as an intact 50 mg Cozaar® tablet (of the same batch) encapsulated in a gelatin capsule

**INVESTIGATOR:** Lars-Goran Nilsson, MD
**STUDY CENTER:** Quintiles AB, Phase I Services, Islandsgatan 2, S-753 18 Uppsala, Sweden
**STUDY PERIOD:** September 23 – October 22, 1997

**OBJECTIVES:** To assess the bioequivalence of the standard commercial losartan tablets compared to the over-encapsulated losartan tablets that were used for blinding purposes in the comparative efficacy studies.

**DESIGN:** open, randomized, single-dose, two-way, crossover investigation, with a washout period of 6-14 days between the dose.

**POPULATION:** Forty healthy adults (27 males, 13 females) completed the study. The demographics are shown in the table below. All subjects were Caucasian.

***Table 5. Demographics – Bioavailability study***

| | **Range (mean ± SD)** |
|---|---|
| Age (years) | 20-33 (24 ± 3) |
| Height (cm) | 161-196 (178 ± 8) |
| Weight (kg) | 57-90 (74 ± 9) |

**DURATION:** One day for the treatment (x 2 treatments) with a 6-14 day washout between treatments

**PROCEDURE:** Subjects were randomized to one of two treatments and then crossed over to the other treatment. OTC and prescription drugs were not allowed one and two weeks, respectively, prior to dosing and throughout the entire study, with the exception of paracetamol for occasional severe pain.

**TREATMENT:** The study drug was administered in the morning (~ 8 am) with 240 mL of room temperature water. It was not mentioned if the patient was in the fasted state.

**LOT:**
**TEST FORMULATION (ET=ENCAPSULATED TABLET)**
A commercially available immediate release (IR) losartan 50 mg tablet (Cozaar®) manufactured by Merck and Co (Batch no HE 303190) was enclosed in rapidly disintegrating opaque gelatin capsule. The remaining space was filled with microcrystalline cellulose, without further manipulation of the marketed tablet by the company Unival, United Kingdom. The capsules were designated Batch no. H 1164-01-03-01.

**REFERENCE FORMULATION (ST=STANDARD TABLET)**
A commercially available immediate release (IR) losartan 50 mg tablet (Cozaar®) manufactured by Merck and Co (Batch no HE 303190) was designated Batch number H 1339-01-01-01 at Astra.

**LOSARTAN ASSAY:** Plasma concentrations of losartan and EXP 3174 were determined by liquid chromatography with fluorescence detection at Bioanalytical Chemistry, Astra Hassle AB, Molndal, Sweden. The intra-day CV% is reported for precision. Linearity was defined as a maximum deviation of 15 % from nominal concentration.

***Table 6. Assay quality***

| | Precision (%) | Accuracy (%) | Sensitivity (ng/mL) | Linearity (ng/mL) |
|---|---|---|---|---|
| Losartan | CV < 6.4 % | Within 10 % | 4.3 | 4.3 – 602 |
| EXP 3174 | CV < 4.5 % | Within 13 % | 1.7 | 1.7 – 467 |

**PHARMACOKINETICS:** Since losartan and its active metabolite, EXP 3174 are responsible for the antihypertensive activity, blood samples for determination of both in plasma were drawn pre-dose and post-dose for up to 36 hours in each treatment period. Samples were drawn at the following times: pre-dose and 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 18, 24, 30 and 36 hours post dose.

**STATISTICS:** The variables AUC and Cmax were analyzed by ANOVA on a log scale corresponding to the two-way cross-over design with factors for sequence, period, treatment and subject-within sequence. The anti-logarithms of the estimates and 90% confidence intervals for the ratio of the true treatment medians were determined. Descriptive statistics were calculated for all pharmacokinetic parameters.

The within-subject standard deviation for ln (AUC) was predicted to be 0.19 and for ln (Cmax) to be 0.25. Thirty-eight subjects would demonstrate bioequivalence with 90% power for AUC and 70% power for Cmax. The true mean AUC and Cmax were assumed to differ by at most 10%, and the significance level was set to 0.05.

**PHARMACOKINETIC ANAYLSIS:** Noncompartmental analysis was performed using WinNonlin version 1.1. Plasma concentrations below the limit of quantitation were excluded from the pharmacokinetic evaluations except at time points prior to Cmax, where non-detectable concentrations were assigned a value of zero.

**RESULTS:** Forty subjects were randomized and completed the study. The pharmacokinetic parameters for the two formulations were similar (see Table below). Plasma levels were measurable for 12 hours post dose. The descriptive pharmacokinetic parameters are shown in the table below.

***Table 7. Losartan and metabolite pharmacokinetic parameters for both formulations***

| Parameter | Losartan | | EXP 3174 | |
|---|---|---|---|---|
| | ET | ST | ET | ST |
| $AUC_{0-\infty}$ (ng*h/mL) | 372 ± 124 | 374 ± 120 | 1952 ± 568 | 1931 ± 629 |
| $AUC_{0-t}$ (ng*h/mL) | 354 ± 125 | 358 ± 120 | 1923 ± 564 | 1903 ± 625 |
| Cmax (ng/mL) | 206 ± 108 | 204 ± 127 | 248 ± 96 | 243 ± 94 |
| Tmax (h) | 1.1 ± 0.5 | 1.1 ± 0.6 | 3.8 ± 0.6 | 4.0 ± 1.1 |
| T ½ (h) | 2.1 ± 0.6 | 2.0 ± 0.5 | 6.6 ± 0.7 | 6.3 ± 0.8 |

Mean ± SD
ET = encapsulated tablet
ST = standard tablet

Plasma concentrations of losartan and metabolite are shown in the two figures below. The standard deviation bar that is going up (T) refers to the encapsulated tablet, and the standard deviation bar that is going down (⊥) refers to the standard tablet.

***Figure 1. Losartan plasma concentrations for both formulations***

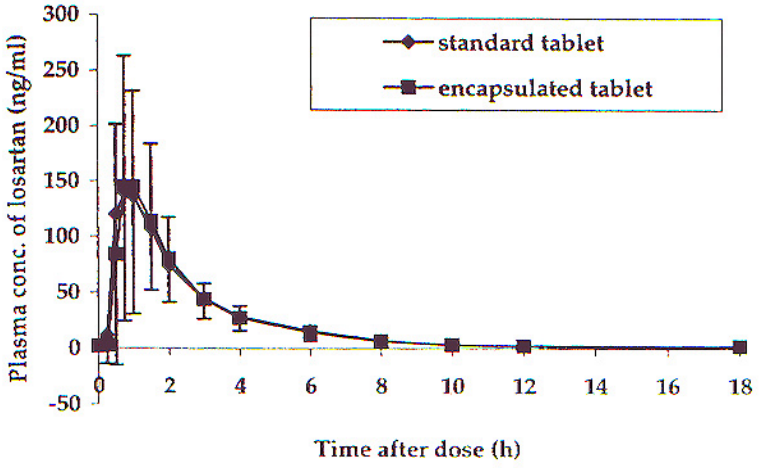
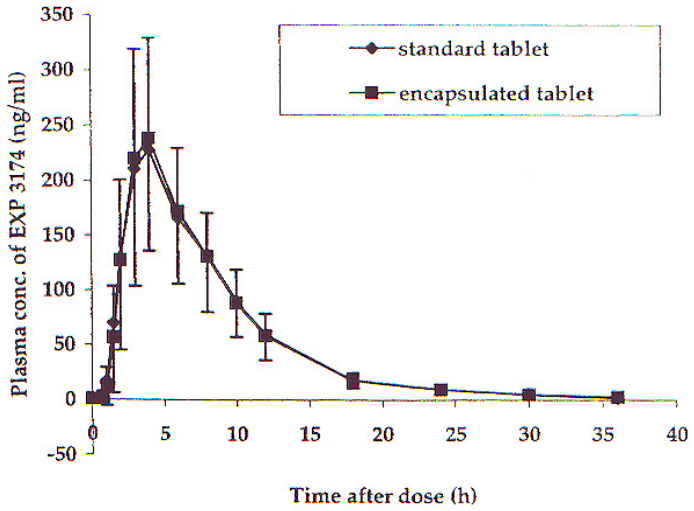



***Figure 2. EXP 3174 plasma concentrations for both formulations***



The two formulations were bioequivalent based on the point estimates and 90% confidence intervals for Cmax and AUC.

***Table 8. Least squares estimates and 90% CI for the ratio of treatment medians (encapsulated/standard tablet) for losartan and metabolite***

| | Losartan | | EXP 3174 | |
|---|---|---|---|---|
| | Estimate | 90% CI | Estimate | 90% CI |
| $AUC_{0-\infty}$ | 1.00 | 0.94 – 1.05 | 1.02 | 0.98 – 1.07 |
| $AUC_{0-t}$ | 0.99 | 0.93 – 1.05 | 1.02 | 0.98 – 1.07 |
| Cmax | 1.04 | 0.93 – 1.17 | 1.03 | 0.97 – 1.10 |

**REVIEWER'S COMMENTS:** The study was only powered at 70% for Cmax. However, the within subject standard deviation (0.31) for Cmax was larger in this study population than that used to calculate 70% power to detect a difference with respect to Cmax. Thus, the study had less than 70% power to detect a difference in Cmax.

The within subject standard deviations was 0.15 for ln-transformed $AUC_{0-\infty}$. Thus, this study population had less variability in AUC than that used to calculate 90% power to detect a difference in $AUC_{0-\infty}$.

Despite being under-powered to detect a significant difference in Cmax (yet over-powered to detect a difference in $AUC_{0-\infty}$) between the two formulations, the sponsor was able to demonstrate bioequivalence between the two formulations since the 90% confidence intervals for both AUC and Cmax were within the accepted criteria of 80-125%.

**CONCLUSION:** The encapsulated losartan is bioequivalent to commercially available losartan.

**STUDY REPORT:** SH-AHC-0009 ITEM-VOLUME-PAGE: 006-001-016 TO 347
**TITLE:** Pharmacokinetics of candesartan cilexetil in patients with moderate to severe impairment of liver function

**INVESTIGATOR:** Gertraud Haug-Pihale, MD, PhD
**STUDY CENTER:** APEX GmbH, Landsbergerstr, 476, D-81241 Munchen, Germany
**STUDY PERIOD:** February 13, 1997 to April 30, 1997 (first enrolled / last completed)

**OBJECTIVES:** Given a single candesartan cilexetil 16 mg dose in patients with moderate to severe liver function, the purposes of this study were:

- To document the pharmacokinetics and
- To evaluate the inactive metabolite (MII) accumulation and elimination of candesartan

A secondary objective was to evaluate the safety and tolerability of candesartan cilexetil.

**DESIGN:** open-label, single dose

**POPULATION:** Twelve patients with mild to moderate liver impairment, defined by the Child Pugh score (CP), and twelve healthy volunteers matched by age, gender and weight were included in the study. Six patients had mild liver impairment (CP = A) and six patients had moderate liver impairment (CP = B).

Participants included Caucasian men (22) and women (2), with a mean ± SD age of 56 ± 6 years, weight of 80 ± 17 kg and height of 175 ± 8 cm.

Patients with encephalopathy greater than Grade II or patients with severe ascites were excluded.

**DURATION:** This was an acute single dose study.

**PROCEDURE:** Patients were screened and severity of liver disease was determined according to the Child-Pugh classification system (see table below). Patients had verified liver cirrhosis by biopsy or a caffeine clearance ≤ 0.8 mL/min/kg. A sonography, aminopyrine breath test and the indocyanine green test were performed.

***Table 9. Child-Pugh (CP) 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 |

CP A = 5-6 points, CP B = 7-9 points, CP C = 10-15 points

Twelve healthy volunteers matched by age, gender and weight were also included in the study.

All participants were given one dose of candesartan and blood samples were drawn at pre-specified times for 36 hours post-dose. Participants were allowed to leave the clinic after the 24 hour blood draw, but had to return for the last blood draw at 36 hours post-dose.

**CONCOMITANT MEDICATIONS:** Medications considered necessary for the patient could be given at the discretion of the investigator. Drugs not allowed included:

- Vasodilators or vasoconstrictors (e.g., theophylline, papaverine, TCA, neuroleptics)
- Sympathicomimetics nasal drugs
- Anti-arrhythmics
- NSAIDs with the exception of aspirin
- Chronic use of steroids
- Immunosuppressives or cytotoxics
- Potassium supplements
- Cimetidine

**TREATMENT:** A single dose of candesartan cilexetil 16 mg was administered with 240 mL of water in the morning.

**FORMULATION:**
Immediate release candesartan cilexetil tablet 16 mg
Batch no H1191-01-01-01
Manufactured at Astra Production Tablets AB, Sodertalje, Sweden

**ASSAY:** Plasma specimens were analyzed for the active metabolite, candesartan (MI, CV-11974) and the inactive metabolite MII (CV-15959) using liquid chromatography with fluorescence detection. The assay quality are shown in the table below for candesartan and M II.

***Table 10. Assay quality***

| | Precision (%) | Accuracy (%) | Sensitivity (ng/mL) | Linearity (ng/mL) |
|---|---|---|---|---|
| Candesartan | CV < 5.5 % | Within 11 % | 0.88 | 0.88 – 396 |
| M II | CV < 6.1 % | Within 11 % | 1.24 | 1.24 – 396 |

**PHARMACOKINETICS:** Blood samples for determination of candesartan and MII in plasma were drawn predose and at the following times post-dose: 1, 2, 3, 4, 5, 6, 8, 10, 12, 24 and 36 hours.

**STATISTICS:** All variables were analyzed on a log scale. For each variable, the mean and a 95% confidence interval were calculated. The antilogarithms of these results are presented, i.e., estimates and confidence limits for the true group median.

Matched pairs were used for comparing the two groups. For each variable and for each matched pair, the difference in the log values between the patient and the healthy volunteer was calculated. For each variable, the mean of all differences was calculated. The differences between patient and healthy volunteer in all matched pairs and Student's t-distribution were used for inference.

**PHARMACOKINETIC ANAYLSIS:** Non-compartmental analysis using WinNonlin version 1.1 was used to estimate the usual PK parameters.

**RESULTS:** Patients had a statistically significant increase of 78% in candesartan $AUC_{0-\infty}$ and 64% in candesartan Cmax compared to volunteers. (See table below.) Half-life was similar in both groups (approximately 9 hours). Cmax was reached in approximately 4 hours in both groups.

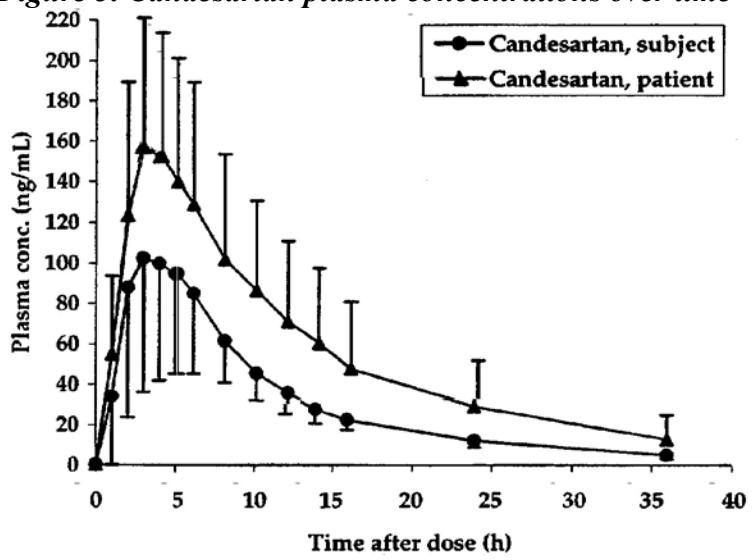
***Table 11. Candesartan PK parameters of hepatic impairment patients and volunteers***

| Parameter | Group | Estimate (95% CI) | Estimate (95% CI) Ratio patient:volunteer | p-value |
|---|---|---|---|---|
| $AUC_{0-\infty}$ (ng*h/mL) | Patient | 2021 (1490, 2739) | 1.78 (1.14, 2.78) | 0.016* |
| | Healthy volunteer | 1135 (900, 1430) | | |
| Cmax (ng/mL) | Patient | 156 (116, 208) | 1.65 (1.04, 2.61) | 0.036* |
| | Healthy volunteer | 95 (65, 138) | | |

* statistically significant

The candesartan plasma concentration versus time curve is shown in the figure below.

***Figure 3. Candesartan plasma concentrations over time***



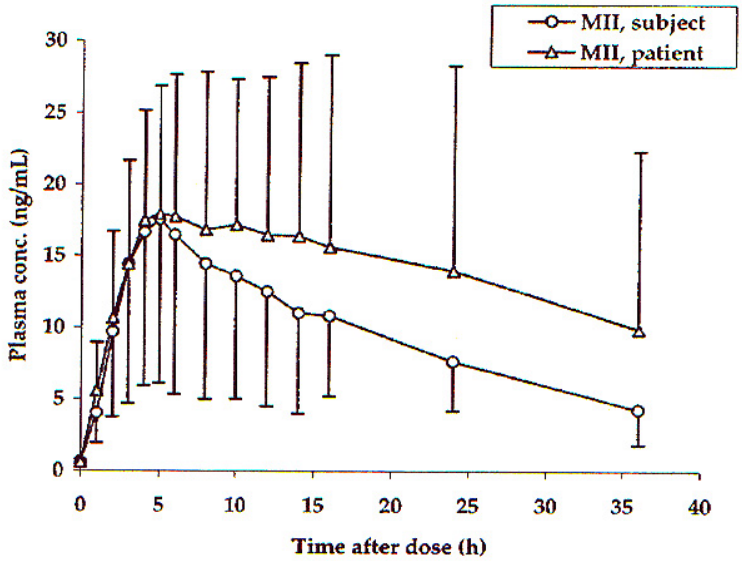

Slight insignificant increases in the inactive metabolite $AUC_{0-t}$ and Cmax were observed for patients compared to volunteers. (See table below.) The residual area for MII $AUC_{0-\infty}$ was greater than 20 % for several patients and volunteers, so the results were not presented.

***Table 12. MII PK parameters of hepatic impairment patients and volunteers***

| Parameter | Group | Estimate (95% CI) | Estimate (95% CI) Ratio patient:volunteer | p-value |
|---|---|---|---|---|
| $AUC_{0-t}$ (ng*h/mL) | Patient | 395 (253, 614) | 1.30 (0.73, 2.28) | 0.338 |
| | Healthy volunteer | 305 (223, 417) | | |
| Cmax (ng/mL) | Patient | 18.4 (13.0, 25.8) | 1.18 (0.67, 2.07) | 0.536 |
| | Healthy volunteer | 15.6 (10.4, 23.5) | | |

The MII plasma concentration versus time curve is shown in the figure below.

***Figure 4. MII plasma concentrations over time***




The sponsor conducted a post-hoc analysis comparing the hepatic impairment groups to volunteers. Patients with mild liver impairment had a 30% increase in candesartan $AUC_{0-\infty}$ and a 56% increase in candesartan Cmax compared to healthy volunteers. Patients with moderate liver impairment had a 145% increase in candesartan $AUC_{0-\infty}$ and a 73% increase in candesartan Cmax compared to healthy volunteers. (See Table below.)

***Table 13. Candesartan PK parameters of hepatic impairment patients and volunteers***

| Parameter | Group | Estimate (95% CI) | Ratio group:volunteer | p-value |
|---|---|---|---|---|
| $AUC_{0-\infty}$ (ng*h/mL) | Mild (CP A) | 1730 (1160, 2578) | 1.30 (0.70, 2.38) | 0.324 |
| | Healthy volunteer | 1335 (869, 2051) | | |
| | Moderate (CP B) | 2361 (1327, 4200) | 2.45 (1.16, 5.14) | 0.027* |
| | Healthy volunteer | 965 (745, 1250) | | |
| Cmax (ng/mL) | Mild (CP A) | 182 (122, 272) | 1.56 (0.80, 3.07) | 0.150 |
| | Healthy volunteer | 117 (57, 237) | | |
| | Moderate (CP B) | 133 (79, 245) | 1.73 (0.71, 4.24) | 0.174 |
| | Healthy volunteer | 77 (48, 122) | | |

* statistically significant
CP = Child Pugh

Safety

Patients with impaired liver function reported most of the adverse events (20 out of 22 reported adverse events). Adverse events that were attributed to drug included tiredness, dizziness and headache. These were reported from a total of four participants. The table below shows the number of participants and reported adverse events.

***Table 14. Reported adverse events***

| Run-in | n | Dose to 36 h post dose | n | > 36 hours post-dose | n |
|---|---|---|---|---|---|
| **Patients** | | | | | |
| Respiratory infection | 2 | Fatigue | 2 | Accident | 1 |
| Coughing | 1 | Bronchitis | 1 | Bronchitis | 1 |
| Dysphonia | 1 | Coughing | 1 | Coughing | 1 |
| | | Dizziness | 1 | Dizziness | 1 |
| | | Dysphonia | 1 | Dysphonia | 1 |
| | | Respiratory infection | 1 | Erysipelas | 1 |
| | | | | Leukocytosis | 1 |
| | | | | Respiratory infection | 1 |
| **Healthy volunteers** | | | | | |
| | | Headache | 1 | Dizziness | 1 |

**CONCLUSION:** The sponsor concludes that in patients with mild liver impairment there is no need for dosage adjustment. In patients with moderate liver impairment, the dose should be initiated low and slowly titrated until an antihypertensive effect is achieved.

**REVIEWER'S COMMENTS:**

The control group was similar in age, gender and race to the hepatic impairment patients.

Since the kinetics of candesartan and its metabolite are linear, single dose should predict multiple doses. Thus, a single dose study for candesartan is appropriate.

Patients with severe hepatic impairment were not included in this study.

**REVIEWER'S CONCLUSIONS:** Patients with mild hepatic impairment do not need the candesartan dose adjusted. Patients with moderate hepatic impairment should be started on a lower dose of candesartan, because of the 145% increase in AUC, and slowly titrated to blood pressure response. The Office of Clinical Pharmacology and Biopharmaceutics' agrees with most of the sponsor's proposed labeling, but also recommends the following marked labeling changes:

- **Special Populations**

*Hepatic Insufficiency:* The pharmacokinetics of candesartan were compared in patients with mild and moderate hepatic impairment to matched healthy volunteers following a single oral dose of 16 mg candesartan cilexetil. The increase in AUC for candesartan was 30% in patients with mild hepatic impairment (Child Pugh A) and 145% in patients with moderate hepatic impairment (Child Pugh B). The increase in Cmax for candesartan was 56% in patients with mild hepatic impairment and 73% in patients with moderate hepatic impairment. The pharmacokinetics after candesartan cilexetil administration have not been investigated in patients with severe hepatic impairment. No initial dosage adjustment is necessary in patients with mild

hepatic impairment. In patients with moderate hepatic impairment, ATACAND should be initiated at a lower dose (see DOSAGE AND ADMINSTRATION).

- **PRECAUTIONS**

**Impaired Hepatic Function**

Based on pharmacokinetic data that demonstrate significant increases in candesartan AUC and Cmax in patients with moderate hepatic impairment, a lower initial dose should be used for patients with moderate hepatic impairment. (see DOSAGE AND ADMINISTRATION, and CLINICAL PHARMACOLOGY, Special Populations).

- **DOSAGE AND ADMINISTRATION**

No initial dosage adjustment is necessary for elderly patients, for patients with mildly impaired renal function, or for patients with mildly impaired hepatic function (see CLINICAL PHARMACOLOGY , Special Populations ). In patients with moderate hepatic impairment, ATACAND should be initiated at 8 mg and titrated to response. (See CLINICAL PHARMACOLOGY, Special Populations).