

AstraZeneca LP

NDA 20-838/S-015

ATACAND[®] (candesartan cilexetil)

Background Information

Cardiovascular and Renal Drugs Advisory Committee Meeting

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Special Term	Explanation
ACE	Angiotensin converting enzyme
AE	Adverse event
ALAT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ARB	Angiotensin II receptor blocker
ASAT	Aspartate aminotransferase
AUC	Area under the curve
BID	Twice daily
BP	Blood pressure
bpm	Beats per minute (heart rate)
CFR	Code of Federal Regulations
C _{max}	Maximum plasma concentration
CAD	Coronary artery disease
CI	Confidence interval
CRF	Case report form
DBP	Diastolic blood pressure
DDMAC	Division of Drug Marketing, Advertising, and Communications
dL	Deciliter
ECG	Electrocardiogram
Hb	Hemoglobin
HCT	Hematocrit
Hg	Mercury
HR	Heart rate
ITT	Intent-to-treat
kg	Kilogram
L	Liter
LOCF	Last observation carried forward
mg	Milligram
mL	Milliliter
mm	Millimeter

ODEI	Office of Drug Evaluation I
QD	Once daily
RAS	Renin-angiotensin system
SAE	Serious adverse event
SBP	Systolic blood pressure
SEM	Standard Error of the Mean
SD	Standard deviation

1.0 PURPOSE

This document summarizes information to support a change in the current labeling for ATACAND® (candesartan cilexetil) tablets. AstraZeneca LP understands that the Division of Cardio-Renal Drug Products has asked the Cardiovascular and Renal Drugs Advisory Committee to comment about this revision to the *Clinical Trials* subsection of CLINICAL PHARMACOLOGY, which presently reads as follows in the proposed labeling for Supplement-015:

“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 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. In these studies, both agents were well tolerated.”

Specifically, this document describes the CLAIM program, which includes two clinical studies (Protocols 230 and 231) of forced-titration design that were conducted in consultation with FDA along with other supporting studies to evaluate the antihypertensive efficacy of candesartan cilexetil in comparison to losartan at the doses recommended for use in patients with hypertension.

AstraZeneca conducted four clinical studies and a bioequivalence study to support the evaluation of the antihypertensive efficacy of candesartan cilexetil in comparison to losartan as follows:

- Protocols 230 and 231 are two identical studies titled “Evaluation of the Antihypertensive Efficacy of Candesartan Cilexetil in Comparison to Losartan: A Multicenter, Double-blind, Randomized, Parallel-group, Forced-titration Study”; the two studies comprise the CLAIM program and are described in the proposed labeling above
- Protocol 175 is a titration-to-effect study titled “Evaluation of the Antihypertensive Effect of Candesartan Cilexetil in Comparison to Losartan: A Double-blind, Multicenter, Parallel Design, Randomized Study”, also known as the CANDLE study
- Protocol SH-AHM-0001 is a starting-dose comparison study titled “The Antihypertensive Effect of Candesartan Cilexetil (8, 16 mg) Once Daily, in Comparison With Losartan (50 mg) Once Daily, and Placebo”
- Protocol SH-AHC-0015 is a bioequivalence study titled “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 Gelatine Capsule”

AstraZeneca proposes to describe the CLAIM program in the labeling within the *Clinical Trials* subsection of CLINICAL PHARMACOLOGY section based on the following rationale:

- The results of the CLAIM program demonstrate substantial evidence of superior antihypertensive efficacy of candesartan cilexetil versus losartan. Both of these forced-titration studies demonstrated statistically significant differences in reduction of blood pressure in favor of candesartan cilexetil versus losartan at the once-daily maximum dose approved for use in the treatment of hypertensive patients.

- This is clinically meaningful information that is relevant to the care of individual patients and it has important public health implications. For example, epidemiologic and clinical intervention studies have demonstrated the benefit of a 2 mm Hg lower diastolic blood pressure. This equates to a 6% reduction in coronary heart disease risk and a 15% stroke risk reduction.
- Inclusion of these data in the label will ensure an enduring and convenient record for prescribers of prescription pharmaceuticals.

2.0 INTRODUCTION

ATACAND® (candesartan cilexetil) is a prodrug that is hydrolyzed during absorption from the gastrointestinal tract to candesartan, a selective AT₁ subtype angiotensin II receptor antagonist. Candesartan cilexetil is currently approved for the treatment of hypertension in adults in many countries and was approved for the treatment of hypertension in the United States in June 1998 under the trademark ATACAND®. The current labeling for ATACAND® is provided in Appendix 1. ATACAND® may be used alone or in combination with other antihypertensive agents. Its blood pressure-lowering effect is dose related over the range of 2 to 32 mg. The usual recommended starting dose is 16 mg once daily when used as monotherapy in patients who do not suffer volume depletion. ATACAND® can be administered once or twice daily with total daily doses ranging from 8 to 32 mg.

2.1 Regulatory History

In August 1998, AstraZeneca met with representatives of the Office of Drug Evaluation I (ODEI), representatives from the Division of Drug Marketing, Advertising and Communications (DDMAC), and representatives from the Division of Cardio-Renal Drug Products regarding the design of studies with ATACAND® to support a claim of superiority in regard to blood pressure-lowering effect over losartan used as monotherapy. The purpose of this meeting was to obtain guidance about the potential use of two comparative studies: Study 175 (a titration-to-effect study) and Study SH-AHM-0001 (a starting-dose comparison study). For Study SH-AHM-0001, the Agency commented that the starting dose is an arbitrary point that does not represent how the drugs would perform over their dose range. This study, therefore, does not provide a meaningful comparison of the drugs. In regard to the titration-to-effect Study 175, the Agency stated that it was not a forced-titration study

design and, consequently, only the poor responders would be titrated to the highest dose of the drugs in this study. The Agency concluded this meeting with the following requirements for AstraZeneca:

- Establish bioequivalence of the test drug
- To demonstrate superiority of ATACAND[®] over a comparator drug, several different doses of each drug would have to be studied, including the maximum once-daily doses approved for use in the treatment of hypertension
- Results must be statistically significant and should be replicated in adequate and well-controlled trials
- The limitations of the trials should be prominently disclosed. For example, if only one dosing regimen is studied, such as once daily, the dosing regimen should be clearly stated
- Examples of acceptable designs for comparative trials would be parallel dose-response or forced-titration studies, examining the response rates over the dose ranges of the drugs, focusing on the maximum dose of the comparator drugs

AstraZeneca submitted a draft protocol of a forced-titration study design late in 1998 to the Division of Cardio-Renal Drug Products for their review to support the efficacy claims that were proposed by AstraZeneca based on the successful completion of two identically designed, forced-titration studies.

In January 1999, AstraZeneca received suggestions from the Division medical officer concerning this program. No major issues were raised, however, AstraZeneca adopted the suggestion to include peak blood pressure as a prespecified, secondary, potentially confirmatory measure of effect.

In June 1999, AstraZeneca submitted Protocols 230 and 231 (together known as the CLAIM program) to the Division, but the medical reviewer raised questions at this time about the use of these studies to support the proposed efficacy of candesartan cilexetil compared to losartan. Consequently, AstraZeneca asked for a meeting to gain clarification about the acceptability of these comparative protocols.

In July 1999, AstraZeneca met with the Division of Cardio-Renal Drug Products via teleconference. The Division's meeting minutes provided the following conclusions:

- There was no issue with the forced-titration design.
- It was emphasized that unless a placebo arm was added to the study, it would not be possible to comment about the magnitude of the BP reduction between drug A and drug B from baseline, but only that there was greater reduction in BP than the comparator.
- It was further noted that the maximum approved dose of losartan was twice daily and the company was using it once daily in the study.
- In addition, the Division would inform DDMAC that promotional material for ATACAND® should state that the duration of effect of losartan might be shorter than the duration of effect of ATACAND® rather than only a difference in magnitude of effect.

As a result, AstraZeneca initiated the CLAIM program that constitutes two identical forced-titration studies for the comparison of efficacy of candesartan cilexetil versus losartan at the recommended starting dose with forced titration of the dose to the recommended maximum once-daily dose in hypertensive patients in order to support a desired claim of statistically significant blood pressure-lowering effect over losartan as monotherapy treatment.

2.2 Regulatory Precedent

According to 21 CFR 201.56 and 201.57, labeling should provide a concise, accurate summary of evidence supporting effectiveness of the product, which generally means the inclusion of adequate and well-controlled studies that address the effectiveness of the product. Based upon this definition, AstraZeneca proposes to describe the CLAIM program in the labeling within the *Clinical Trials* subsection of the CLINICAL PHARMACOLOGY section for the following reasons:

- (1) These data from two forced-titration studies provide substantial evidence by replication of the statistically significant antihypertensive efficacy of ATACAND[®] compared to losartan at the once-daily maximum dose approved for use in the treatment of hypertensive patients
- (2) This information is clinically meaningful for the treatment of hypertension, which is described in more detail below within Section 7.0 of this document
- (3) Inclusion of the data in the label will ensure there is an enduring and convenient record for prescribers of prescription pharmaceuticals.

As discussed in detail above in Section 2.1 Regulatory History, AstraZeneca reached an agreement with ODEI, DDMAC, and the Division of Cardio-Renal Drug Products concerning the definition of what met the requirements for substantial evidence to support a claim of superiority of efficacy for ATACAND[®] versus losartan. Based on that agreement AstraZeneca took the following actions in response to the requirements identified below in bullet form to develop and conduct adequate and well-controlled studies to compare the efficacy of ATACAND[®] versus losartan:

- **Requirement No. 1: establish bioequivalence of the test drug**
 - *Conducted Protocol SH-AHC-0015, a bioequivalence study, which establishes the bioequivalence of the test drug*

- **Requirement No. 2: to demonstrate superiority of ATACAND[®] over a comparator drug, several different doses of each drug would have to be studied, including the maximum once-daily doses approved for use in the treatment of hypertension**
 - *Initiated treatment in the CLAIM program at the recommended starting dose of ATACAND[®] 16 mg and losartan 50 mg; forced-titrated the dose to the maximum once-daily dose in hypertensive patients of 32 mg of ATACAND[®] and 100 mg of losartan*

- **Requirement No. 3: results must be statistically significant and should be replicated in adequate and well-controlled trials**
 - *Statistically significant results have been replicated in two adequate and well-controlled trials*

- **Requirement No. 4: the limitations of the trials should be prominently disclosed. For example, if only one dosing regimen is studied, such as once daily, the dosing regimen should be clearly stated**
 - *Proposed labeling states the regimen is once daily (emphasis added by underlining relevant text below) as follows:*

“Two identically designed, concurrently conducted, 8-week, multicenter, double-blind, randomized, forced-titration studies were performed to compare the antihypertensive efficacy of ATACAND and losartan at their once daily maximum doses. ATACAND 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. In these studies, both agents were well-tolerated.”

- **Requirement No. 5: examples of acceptable designs for comparative trials would be parallel dose-response or forced-titration studies, examining the response rates over the dose ranges of the drugs, focusing on the maximum dose of the comparator drugs**
 - *The CLAIM program included two studies of forced-titration design*

In addition to fulfilling the requirements that were agreed upon between AstraZeneca and ODEI, DDMAC, and the Division of Cardio-Renal Drug Products, AstraZeneca proposes to include comparator information from these two identical forced-titration studies in the labeling because it is also consistent with the general requirements of the content and format of labeling for human prescription drugs according to 21 CFR 201.57(c)(3)(v). It states in this section in regard to the INDICATIONS AND USAGE section that “any statements comparing the safety or effectiveness, either greater or less, of the drug with other agents for the same indication shall be supported by adequate and well-controlled studies” Under 21 CFR 201.56(d)(2), the labeling may contain additional section headings, such as “Clinical Studies,” if appropriate and in compliance with 21 CFR 201.57.

AstraZeneca proposes to place the results from the CLAIM program in the *Clinical Trials* subsection of the CLINICAL PHARMACOLOGY section of the label, because it is consistent with the content and placement of comparator information in labeling of other antihypertensive products (refer to Appendix 2). For example, the current labeling for Zestril® (lisinopril), also commercially available as Prinivil® (lisinopril), contains the following text in a subsection of labeling, entitled *Pharmacodynamics and Clinical Effects, Hypertension* under CLINICAL PHARMACOLOGY (refer to Appendix 2), based on data from parallel dose-response studies:

“In controlled clinical studies, ZESTRIL 20-80 mg has been compared in patients with mild to moderate hypertension to hydrochlorothiazide 12.5-50 mg and with atenolol 50-200 mg; and in patients with moderate to severe hypertension to metoprolol 100-200 mg. It was superior to hydrochlorothiazide in effects on systolic and diastolic pressure in a population that was ¾ Caucasian. ZESTRIL was approximately equivalent to atenolol and metoprolol in effects on diastolic blood pressure, and had somewhat greater effects on systolic blood pressure.”

Other antihypertensive products include claims of “similar” antihypertensive activity in this subsection of labeling (Accupril[®], Altace[®], and Diovan[®], see Appendix 2).

In addition, comparator safety information may be found either in the ADVERSE REACTIONS section of labeling, such as the studies comparing the incidence of cough for Cozaar[®] (losartan potassium) with lisinopril and hydrochlorothiazide, or within the *Clinical Trials* subsection of labeling, such as the studies comparing the incidence of cough for Teveten[®] (eprosartan mesylate) with enalapril. For example, the labeling for Cozaar[®] (losartan potassium) contains comparator information within the ADVERSE REACTIONS section of labeling (refer to Appendix 2):

“Persistent dry cough (with an incidence of a few percent) has been associated with ACE inhibitor use and in practice can be a cause of discontinuation of ACE inhibitor therapy. Two prospective, parallel-group, double-blind, randomized, controlled trials were conducted to assess the effects of losartan on the incidence of cough in hypertensive patients who had experienced cough while receiving ACE inhibitor therapy. Patients who

had typical ACE inhibitor cough when challenged with lisinopril, whose cough disappeared on placebo, were randomized to losartan 50 mg, lisinopril 20 mg, or either placebo (one study, n=97) or 25 mg hydrochlorothiazide (n=135). The double-blind treatment period lasted up to 8 weeks. The incidence of cough is shown below.

Study 1 [†]	HCTZ	Losartan	Lisinopril
Cough	25%	17%	69%
Study 2 ^{††}	Placebo	Losartan	Lisinopril
Cough	35%	29%	62%

† Demographics = (89% Caucasian, 64% female)

†† Demographics = (90% Caucasian, 51% female)

These studies demonstrate that the incidence of cough associated with losartan therapy, in a population that all had cough associated with ACE inhibitor therapy, is similar to that associated with hydrochlorothiazide or placebo therapy.”

According to the Division’s memorandum of review of NDA 20-386 in 1995 for Cozaar[®], the Division specified that two studies would be required to substantiate the above claim about a lack of cough as a side effect for losartan. The primary objective of the two controlled studies described above from the label for Cozaar[®] was to evaluate the difference in the incidence of cough experienced by hypertensive patients rather than to evaluate the antihypertensive products’ ability to lower BP more effectively than another agent. While the objective for the two controlled studies for ATACAND[®] versus losartan is different from the primary objective of the two controlled studies for Cozaar, the proposed labeling is similar in

that it focuses on the primary objective of these two studies and in addition provides a brief statement of the safety results, as both drugs were well tolerated. In summary, the proposed labeling for ATACAND[®] is consistent in content and placement of the text within labeling for a variety of antihypertensive products.

Lastly, labeling is an enduring record of the relevant safety and effectiveness of a drug that must be maintained as long as the product is commercially available from the intellectual property holder and/or its generic manufacturer. AstraZeneca also proposes to describe the CLAIM program in the labeling within the *Clinical Trials* subsection of CLINICAL PHARMACOLOGY section because the inclusion of the data in the label will ensure there is an enduring and convenient record for prescribers of prescription pharmaceuticals.

In conclusion, AstraZeneca proposes to describe the CLAIM program in the labeling within the *Clinical Trials* subsection of CLINICAL PHARMACOLOGY section for the following reasons:

- These data from two forced-titration studies provide substantial evidence by replication of the statistically significant antihypertensive efficacy of ATACAND[®] compared to losartan at the once-daily maximum dose approved for use in the treatment of hypertensive patients
- The proposed labeling is consistent with the general requirements of the content and format of labeling for human prescription drugs and it is also consistent with approved labeling for other antihypertensive products that include comparator information
- Inclusion of the data in the label will ensure there is an enduring and convenient record for prescribers of prescription pharmaceuticals

- These data also provide clinically meaningful information, which is described in more detail within Section 7.0 of this document below.

3.0 SCIENTIFIC RATIONALE

Hypertension is a powerful, independent, but controllable promoter of cardiovascular disease. Its prevalence is distressingly high, afflicting approximately 50 million Americans.¹ The risk for cardiovascular disease increases incrementally with increases in BP with no clear value delineating “normal” from “abnormal” measurements. As illustrated in the Multiple Risk Factor Intervention Trial (MRFIT), coronary mortality increased 6% to 8% for each 1-mm Hg increment increase in systolic blood pressure.² This also implies that mild hypertension and inadequately controlled hypertension have a substantial impact on cardiovascular disease. One study estimated that mild hypertension accounts for 32% of hypertension-attributable cardiovascular events in elderly men (27% for women) and inadequately controlled hypertension accounted for 33% of cardiovascular events in elderly men (64% in women).³ Therefore, more aggressive treatment³ of mild hypertension as well as improved control in those patients already treated will contribute a substantial clinical benefit.

Reducing elevated BP with antihypertensive drug therapy substantially decreases cardiovascular morbidity and mortality including stroke, coronary events, heart failure, progression in renal failure, and all-cause mortality.⁴ From 1976 to 1994 in the United States, the number of patients with controlled (< 140/90 mm Hg) high BP increased from 10% to 27% which contributed significantly to the improvement in cardiovascular morbidity and mortality rates.⁴ Importantly, even small reductions in blood pressure in a population may translate into measurable public health benefits. Analyses of observational studies and randomized clinical trials suggest that a 2-mm Hg reduction in diastolic BP will translate into a 6% reduction in the risk for coronary heart disease and a 15% reduction in stroke risk for Americans aged 35 to 64 years.⁵ Given the established value of lowering elevated blood

pressure, identifying which antihypertensive drugs are most effective becomes clinically important. Proper identification of the antihypertensive agents most effective at lowering BP in a population is efficiently achieved by means of standardized, well-conducted, comparator trials, which determine the relative efficacy and safety of these agents.

Candesartan, developed by Takeda Chemical Industries Ltd., Japan, is a potent, highly selective AT₁-subtype angiotensin II receptor antagonist that has high affinity to the receptor and is devoid of agonist activity in vitro.⁶ Candesartan exhibits greater affinity (> 10,000-fold) for the AT₁ receptor compared with the AT₂ receptor, and exhibits a slow rate of dissociation from the AT₁ receptor.⁷ The in vitro affinity for the AT₁ receptor by candesartan is 80-fold greater than that observed with losartan, ten-fold greater than the active metabolite of losartan, and seven-fold greater than that observed with angiotensin II.⁷ As demonstrated in preclinical models, there are differentiating pharmacologic, pharmacodynamic and blood pressure lowering effects of candesartan when compared to losartan and EXP-3174 (losartan's active metabolite).⁸ Furthermore, consistent with results from experimental pharmacology, Belz et al⁹ used a quantitative technique in humans to establish that candesartan displayed the highest pharmacological potency (ie, antagonistic activity per mg substance) of the AT₁ receptor blockers tested, including losartan, and in addition a greater number of AT₁ receptors were still bound by candesartan versus losartan after 24 hours. The high-affinity receptor binding and the slow receptor-dissociation rate of candesartan observed in animals¹⁰ and in humans¹¹ is a result of its distinctive receptor-binding characteristics.¹⁰

Preclinical data cited above as well as clinical trial data confirm that candesartan cilexetil is more effective than losartan in blocking the effects of angiotensin II at the AT₁ receptor and in significantly reducing BP. A phase I study indicated that candesartan cilexetil 16 mg

provided greater reductions in BP in normotensive individuals pretreated with a diuretic compared with losartan 50 mg.¹² In addition, three clinical trials in hypertensive patients demonstrated a significantly greater reduction in trough sitting diastolic BP with candesartan cilexetil compared with losartan.¹³⁻¹⁵ The first study was a placebo-controlled comparison of the recommended starting dose of losartan (50 mg once daily) and candesartan cilexetil (16 mg once daily).¹⁵ The second study, a titration-to-effect study, compared the recommended dosing regimens of losartan (50 mg, 100 mg once daily) and candesartan cilexetil (16 mg, 32 mg once daily).¹³ The third study, a double-blind, placebo-controlled, forced-titration study in ambulatory hypertensive patients, compared losartan (50 mg, 100 mg once daily) with candesartan cilexetil (8 mg, 16 mg once daily).¹⁴

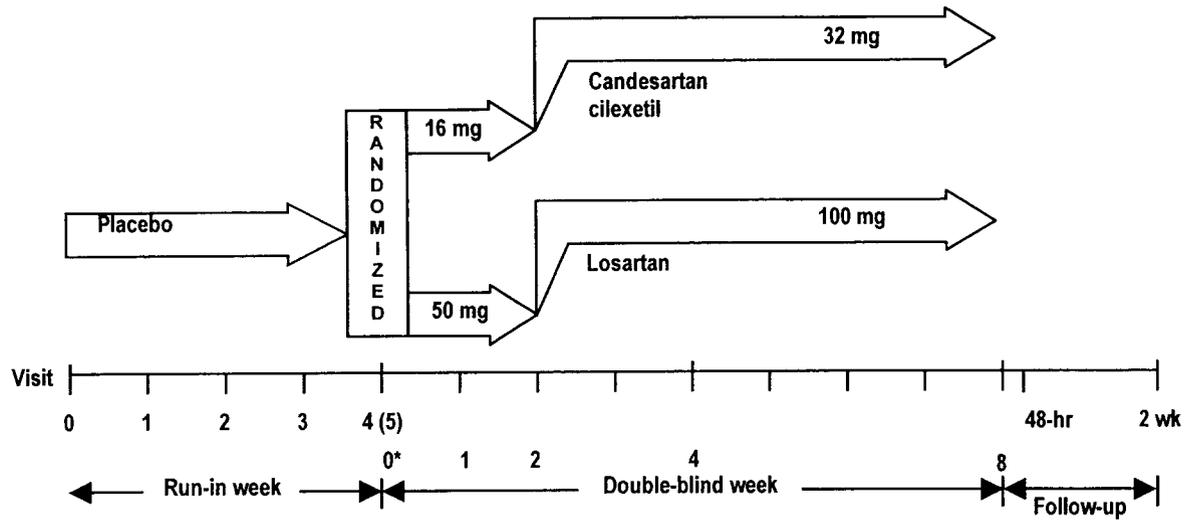
Based on the above considerations, AstraZeneca developed the CLAIM program to test the hypothesis that the receptor-binding properties of candesartan would translate into a greater blood pressure-lowering effect compared with losartan at the highest recommended once-daily doses. This clinical program provides substantial evidence derived from two prospective, adequate, and well-controlled clinical studies in support of the proposed labeling claim.

4.0 THE CLAIM PROGRAM

Two identically designed, concurrently conducted, 8-week, multicenter, double-blind, randomized, forced-dose escalation, parallel-group studies compared the efficacy, safety, and tolerability of candesartan cilexetil versus losartan in hypertensive patients.^{16,17} Study 230 (n = 613) and Study 231 (n = 655) enrolled patients with a sitting diastolic BP of 95 to 114 mm Hg. Patients with any of the following were excluded: secondary hypertension; myocardial infarction, coronary bypass surgery, stroke, or transient ischemic attack within 6 months; percutaneous transluminal coronary angioplasty (PTCA) within 3 months; severe hepatic or renal impairment; hemodynamically significant valvular heart disease or angina pectoris requiring more than short-acting nitrates.

Following a placebo run-in period of 4 to 5 weeks, enrolled patients were randomized to receive 16 mg of candesartan cilexetil or 50 mg of losartan once daily (Figure 1). At double-blind Week 2, doses were increased to 32 mg or 100 mg once daily for candesartan cilexetil or losartan, respectively, for the remaining 6 weeks of the study.

FIGURE 1.—Design of Studies 230 and 231.



*Randomization visit (placebo run-in Week 4 or optional placebo run-in Week 5).

4.1 Primary Objective

The objective of both studies was to evaluate the efficacy of candesartan cilexetil in comparison to losartan forced-titrated to the recommended once-daily maximum dose in hypertensive patients.

4.2 Efficacy Endpoints

Primary measure of antihypertensive efficacy:

- Mean change in trough (24 ± 3 hours after drug administration) sitting diastolic BP from baseline (end of the placebo run-in period/randomization visit) to Double-blind Week 8

Secondary efficacy measures included:

- Mean change from baseline to Week 8 in trough sitting systolic BP

- Mean change from baseline to Week 8 in peak (6 ± 2.5 hours after drug administration) sitting diastolic BP and systolic BP
- Mean change from baseline to a 48-hour post-dose (“missed dose”) visit (after Week 8) in sitting diastolic BP and systolic BP
- Proportion of responders and controlled patients based on trough sitting diastolic BP at Week 8
- Trough to peak ratio for sitting diastolic BP at Week 8

4.3 Summary of Statistical Methods

Statistical analyses were performed based on the following prespecified definitions.

The intent-to-treat (ITT) population was defined as all randomized patients with baseline and at least one post-baseline BP measurement. The primary analysis was conducted in the ITT/LOCF population. Patients who withdrew from the trial prior to double-blind Week 8 were included using their last available “on treatment” BP measurement. Secondary efficacy analyses were conducted with the ITT population using actual data.

The safety population included all patients who received at least one dose of study medication and received at least one post-baseline contact with an investigative site.

An analysis of covariance (ANCOVA) was employed for the primary efficacy analysis to ascertain whether candesartan cilexetil 16 mg forced-titrated to 32 mg was different from losartan 50 mg forced-titrated to 100 mg with respect to reducing BP over an 8-week treatment period. To accomplish this comparison, the SAS[®] generalized linear models procedure was utilized with the change from baseline to double-blind Week 8 in trough

sitting diastolic BP as the response variable; with treatment, center, and treatment by center as fixed effects; and with baseline trough sitting diastolic BP as the covariate in the model.

The proportions of patients classified as “responders” or “controlled” based on trough sitting diastolic BP were calculated for each treatment group. “Responders” were defined as patients with either a sitting diastolic BP of < 90 mm Hg or a decrease from baseline in trough sitting diastolic BP of ≥ 10 mm Hg. “Controlled” patients were defined as patients with a sitting diastolic BP of < 90 mm Hg. Responder and control rates were compared by Fisher’s exact test.

Trough-to-peak ratios for sitting diastolic BP were calculated across treatment groups, but were not compared.

Statistical analyses for demographics and adverse events were descriptive.

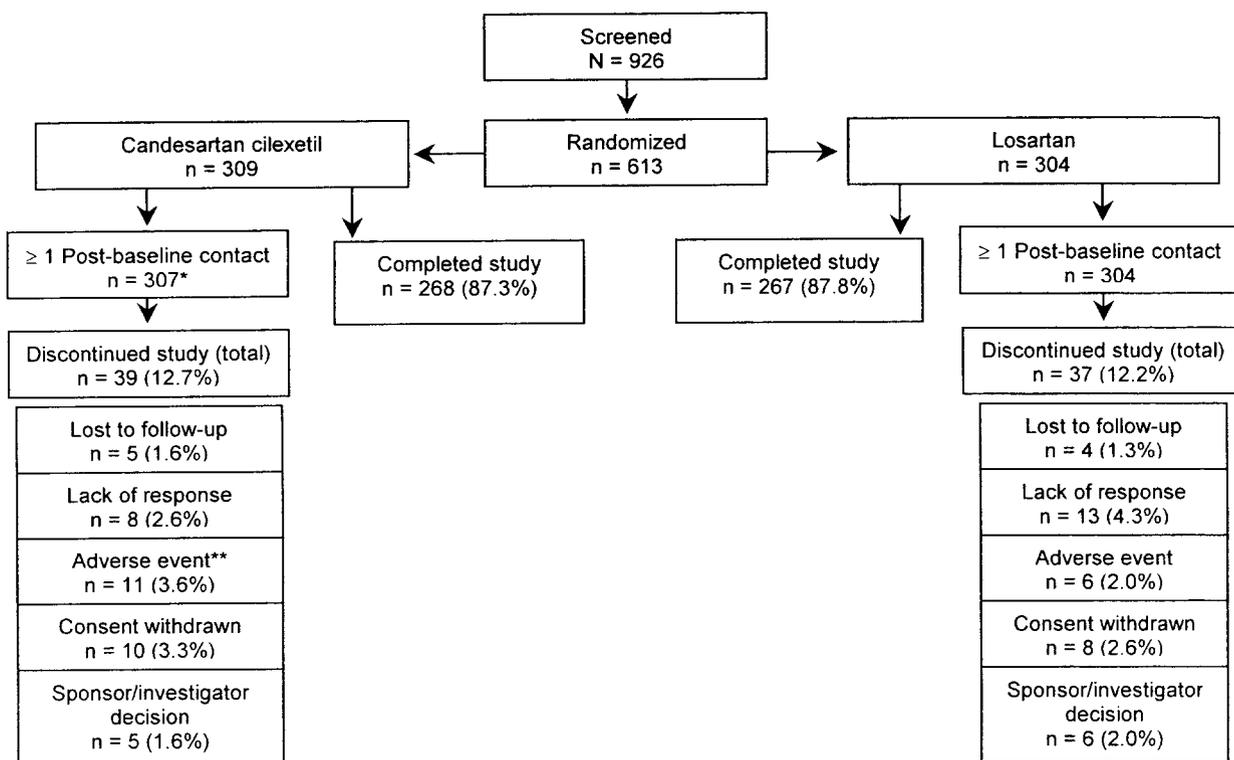
Sample size estimation assumed a standard deviation of 7.5 mm Hg in trough sitting diastolic BP and a two-tailed test ($\alpha = 0.05$). A total sample size of 735 patients provided at least 95% power to detect a true mean difference of 2 mm Hg in diastolic pressure.

4.4 Patient Disposition

In Study 230, as summarized in Figure 2, a total of 926 patients were screened and 613 patients were randomized to candesartan cilexetil or losartan at 72 clinical study sites. Two randomized patients in the candesartan cilexetil group did not return after randomization. Accordingly, a total of 611 randomized patients (candesartan cilexetil group [n = 307]; losartan group [n = 304]) had at least one post-baseline contact and comprised the safety population. Of these patients, 76 (12.4%) discontinued from the study, 39 (12.7%)

candesartan cilexetil-treated and 37 (12.2%) losartan-treated patients. Reasons for premature discontinuations are presented in Figure 2. Thirteen patients (4.3%) treated with losartan discontinued due to the lack of therapeutic response compared with eight patients (2.6%) treated with candesartan cilexetil. Overall, 535 (87.6%) of randomized patients, 268 (87.3%) candesartan cilexetil-treated patients and 267 (87.8%) losartan-treated patients, completed the study.

FIGURE 2.—Disposition of patients in Study 230.



Note: Numbers and percentages of patients who discontinued and completed the study are based on the number of patients who were randomized and had at least one post-baseline contact with the investigator site.

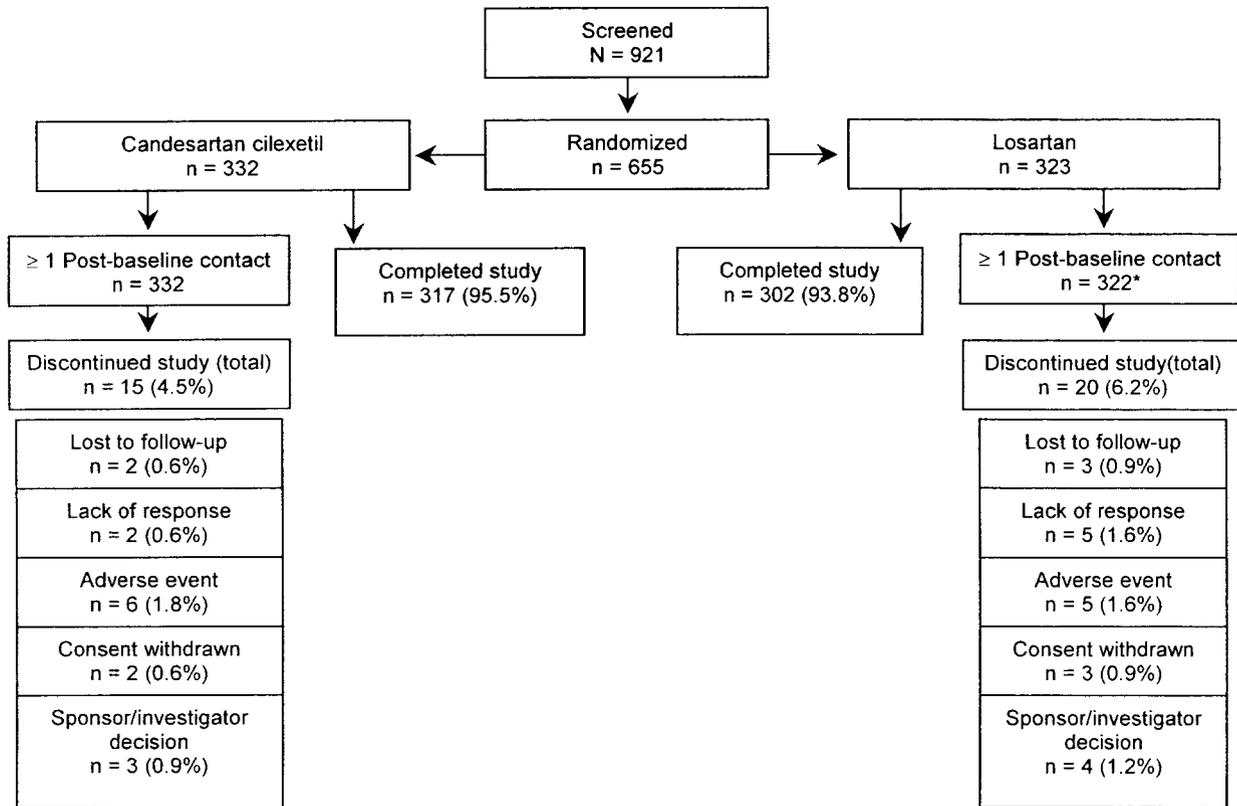
*In Study 230, two patients in the candesartan cilexetil group discontinued without any post-baseline contact with the investigator sites.

**In Study 230, two patients discontinued from the study due to adverse events that occurred during the 2-week safety follow-up period at the end of the study.

In Study 231, 72 clinical study sites screened a total of 921 patients and 655 patients were randomized (Figure 3). One patient, in the losartan treatment group, did not have any post-baseline visits. Accordingly, 654 randomized patients (candesartan cilexetil group [n = 332] and losartan group [n = 322]) had at least one post-baseline contact. Of the 654 patients, a total of 35 (5.4%) discontinued the study, 15 and 20 patients in the candesartan cilexetil and losartan groups, respectively. The proportion of patients discontinuing in the candesartan

cilexetil group (4.5%) was comparable to that observed with the losartan group (6.2%) (Figure 3). Overall, 619 patients (94.6%), 317 candesartan cilexetil-treated patients (95.5%) and 302 losartan-treated patients (93.8%), completed the study.

FIGURE 3.—Disposition of patients in Study 231.



Note: Numbers and percentages of patients who discontinued and completed the study are based on the number of patients who were randomized and had at least one post-baseline contact with the investigator site.

*In Study 231, one patient in the losartan group discontinued without any post-baseline contact with the investigator sites.

4.5 Patient Demographics and Other Baseline Characteristics

In Studies 230 and 231, the two treatment groups were well balanced in key baseline and demographic characteristics (Table 1). The mean age of patients was approximately 55 years, over half were male, nearly 20% were black, and approximately 9% had a history of

diabetes mellitus (57 of 611 in Study 230 and 59 of 654 patients in Study 231). The mean baseline weight was 216.1 pounds and 185.6 pounds for males and females, respectively. In addition, baseline BP was approximately 152/100 mm Hg and hypertension was a long-standing diagnosis (mean duration, approximately ten years).

TABLE 1. Patient Demographics and Other Baseline Characteristics

	Study 230			Study 231		
	Candesartan cilixetil (n = 307)	Losartan (n = 304)	Overall (n = 611)	Candesartan cilixetil (n = 332)	Losartan (n = 322)	Overall (n = 654)
Age (yrs) ^A	55.5 (9.9)	55.1 (11.0)	55.3 (10.5)	54.2 (11.1)	54.1 (10.4)	54.1 (10.8)
Weight (lbs) ^A	204.7 (44.5)	200.6 (41.3)	202.6 (43.0)	205.6 (46.6)	202.6 (42.1)	204.2 (44.4)
Duration of hypertension (yrs) ^A	10.5 (9.4)	10.3 (9.8)	10.4 (9.6)	10.4 (8.9)	10.0 (9.0)	10.2 (9.0)
Sex ^B						
Male	179 (58.3)	179 (58.9)	358 (58.6)	192 (57.8)	188 (58.4)	380 (58.1)
Female	128 (41.7)	125 (41.1)	253 (41.4)	140 (42.2)	134 (41.6)	274 (41.9)
Race ^B						
Non-Black	245 (79.8)	245 (80.6)	490 (80.2)	273 (82.2)	268 (83.2)	541 (82.7)
Black	62 (20.2)	59 (19.4)	121 (19.8)	59 (17.8)	54 (16.8)	113 (17.3)
Baseline trough DBP (mm Hg) ^A	100.4 (4.3)	100.2 (4.3)	100.3 (4.3)	100.1 (3.9)	99.9 (4.2)	100.0 (4.1)
Baseline trough SBP (mm Hg) ^A	153.6 (11.7)	152.2 (12.3)	152.9 (12.0)	152.6 (12.3)	152.0 (12.6)	152.3 (12.4)
Baseline peak DBP (mm Hg) ^A	97.8 (6.1)	97.3 (6.1)	97.5 (6.1)	97.8 (5.8)	97.5 (5.8)	97.6 (5.8)
Baseline peak SBP (mm Hg) ^A	151.5 (11.7)	150.3 (12.6)	150.9 (12.2)	150.7 (12.2)	149.9 (12.7)	150.3 (2.5)

Note: Trough and peak blood pressures captured according to time of placebo dosing during run-in period.

^AExpressed as Mean (SD).

^BExpressed as number (%).

4.6 Efficacy Results: Comparative Efficacy of Candesartan Cilexetil Versus Losartan

In both studies the primary efficacy measure, mean reduction in trough diastolic BP from baseline to Week 8, was significantly greater for candesartan cilexetil. In Study 230, the mean difference in trough diastolic BP favored candesartan cilexetil by 1.5 mm Hg ($p = 0.0411$) and in Study 231 by 2.2 mm Hg ($p = 0.0005$). In addition, there was a consistent and significant mean difference favoring candesartan cilexetil for all secondary efficacy measures (ie, trough systolic BP, peak BPs, and 48-hour washout BPs) summarized in Table 2 and Figures 4 and 5.

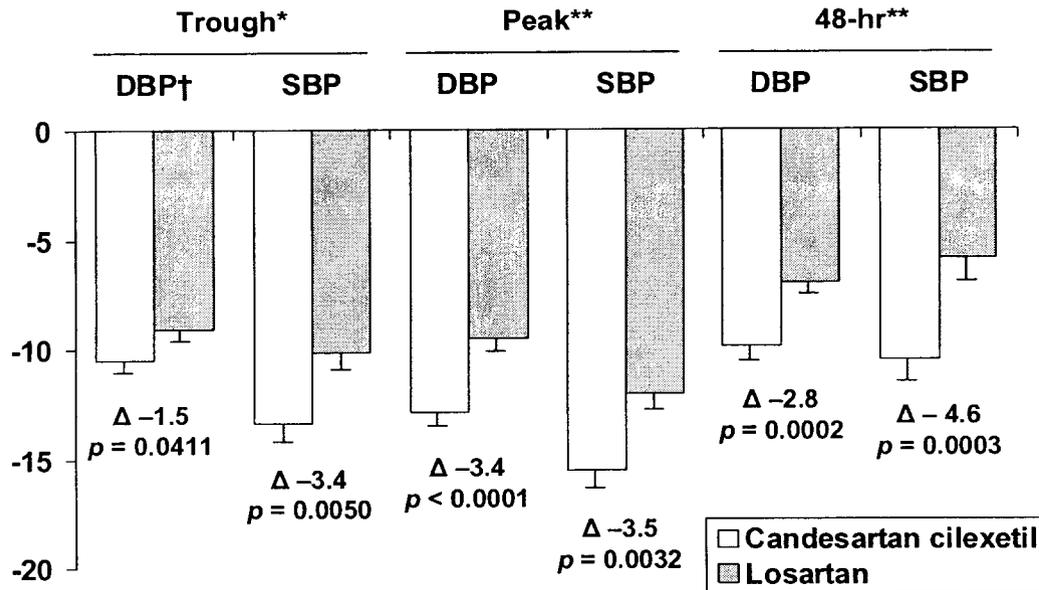
TABLE 2. Least Square Mean Changes[§] in Sitting Blood Pressure From Baseline to Week 8

BP (mm Hg)	Study 230				Study 231			
	Candesartan cilexetil	Losartan	Mean difference	p value	Candesartan cilexetil	Losartan	Mean difference	p value
Primary efficacy endpoint								
Trough DBP*	-10.5	-9.1	-1.5	0.0411	-10.9	-8.7	-2.2	0.0005
Secondary efficacy endpoints								
Trough SBP*	-13.4	-10.1	-3.4	0.0050	-13.3	-9.8	-3.5	0.0007
Peak DBP**	-12.9	-9.5	-3.4	< 0.0001	-11.6	-10.1	-1.5	0.0375
Peak SBP**	-15.5	-12.0	-3.5	0.0032	-15.2	-12.6	-2.6	0.0170
48-hour DBP**	-9.9	-7.0	-2.8	0.0002	-10.2	-6.0	-4.3	< 0.0001
48-hour SBP**	-10.5	-5.9	-4.6	0.0003	-11.2	-5.3	-5.9	< 0.0001

§Adjusted for baseline blood pressure.

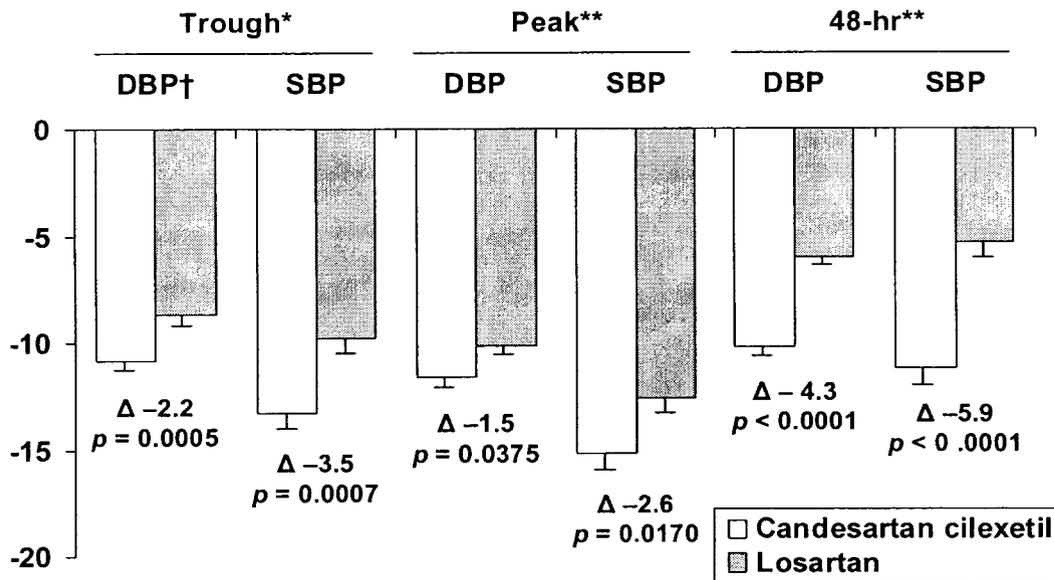
*ITT/LOCF population. **ITT population.

FIGURE 4.—Least square mean changes[§] (SEM) in sitting blood pressure from baseline to Week 8 (Study 230).



§Adjusted for baseline blood pressure.
 * ITT/LOCF population. ** ITT population.
 †Primary endpoint.

FIGURE 5.—Least square mean changes[§] (SEM) in sitting blood pressure from baseline to Week 8 (Study 231).



§Adjusted for baseline blood pressure.
 * ITT/LOCF population. ** ITT population.
 †Primary endpoint.

As noted above, candesartan cilexetil exhibited a statistically significant greater reduction in trough diastolic BP from baseline to Week 8 compared with losartan in Study 230 ($p = 0.0411$) and Study 231 ($p = 0.0005$). The blood pressure-lowering effect by study visit demonstrated that for both Study 230 (Table 3; Figure 6) and Study 231 (Table 4; Figure 7), candesartan cilexetil consistently exhibited greater BP reductions from Week 2 (when doses were up-titrated) to the end of the study.

TABLE 3. Trough Sitting Diastolic Blood Pressure (mm Hg) by Treatment and Visit (Study 230 ITT Population)

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

*Doses were up-titrated at Week 2.

FIGURE 6.—Trough sitting diastolic blood pressure (mm Hg) by treatment and visit (Study 230 ITT population).

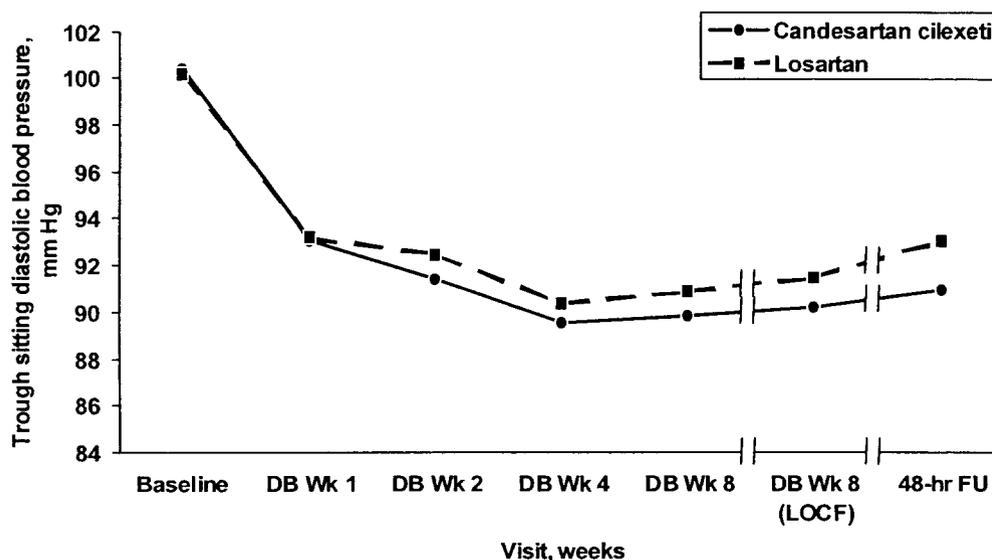
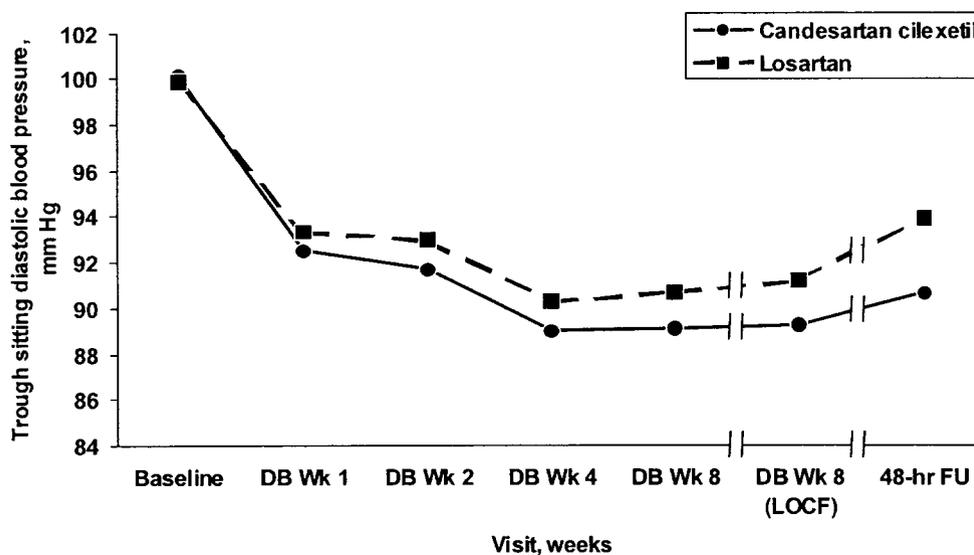


TABLE 4. Trough Sitting Diastolic Blood Pressure (mm Hg) by Treatment and Visit (Study 231 ITT Population)

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

*Doses were up-titrated at Week 2.

FIGURE 7.—Trough sitting diastolic blood pressure (mm Hg) by treatment and visit (Study 231 ITT population).



As summarized in Table 2, for systolic BP candesartan cilexetil exhibited a significantly greater mean reduction compared with losartan in both Study 230 ($p = 0.0050$) and Study 231 ($p = 0.0007$). Candesartan cilexetil also consistently exhibited a greater mean BP reduction in trough sitting systolic BP from Week 2 throughout the study period for both Study 230 (Table 5; Figure 8) and Study 231 (Table 6; Figure 9).

TABLE 5. Trough Sitting Systolic Blood Pressure (mm Hg) by Treatment and Visit (Study 230 ITT Population)

Treatment		Baseline	DB Wk 1	DB Wk 2*	DB Wk 4	DB Wk 8	DB Wk 8 (LOCF)	48-hr FU
Candesartan cilexetil	N	307	304	300	292	284	306	246
	Mean (SD)	153.6 (11.7)	144.0 (14.6)	141.1 (13.0)	139.0 (14.8)	139.6 (15.9)	140.4 (16.8)	142.9 (15.6)
Losartan	N	303	302	297	292	280	303	247
	Mean (SD)	152.2 (12.3)	143.9 (14.2)	142.2 (14.2)	140.4 (14.5)	141.2 (14.4)	142.2 (15.8)	146 (15.7)

*Doses were up-titrated at Week 2.

FIGURE 8.—Trough sitting systolic blood pressure (mm Hg) by treatment and visit (Study 230 ITT population).

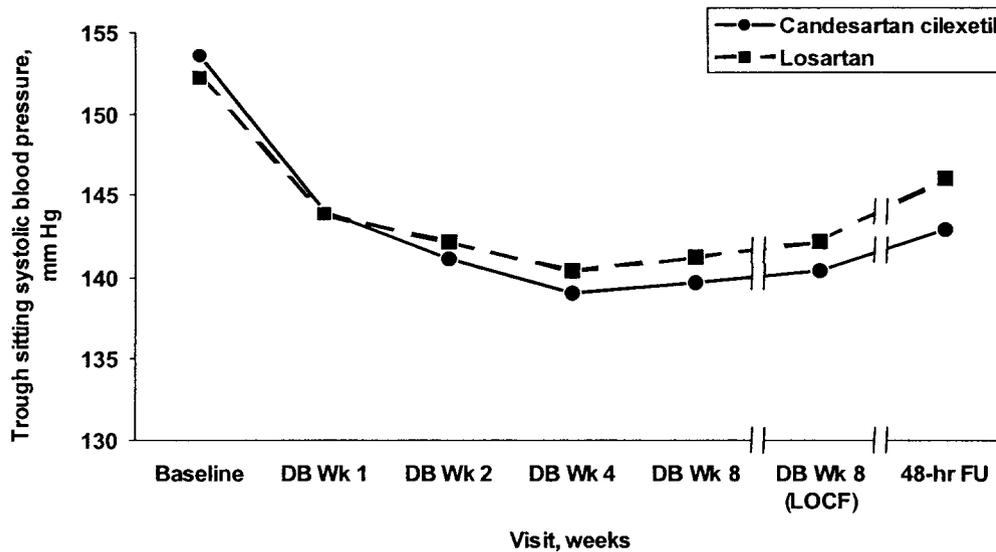
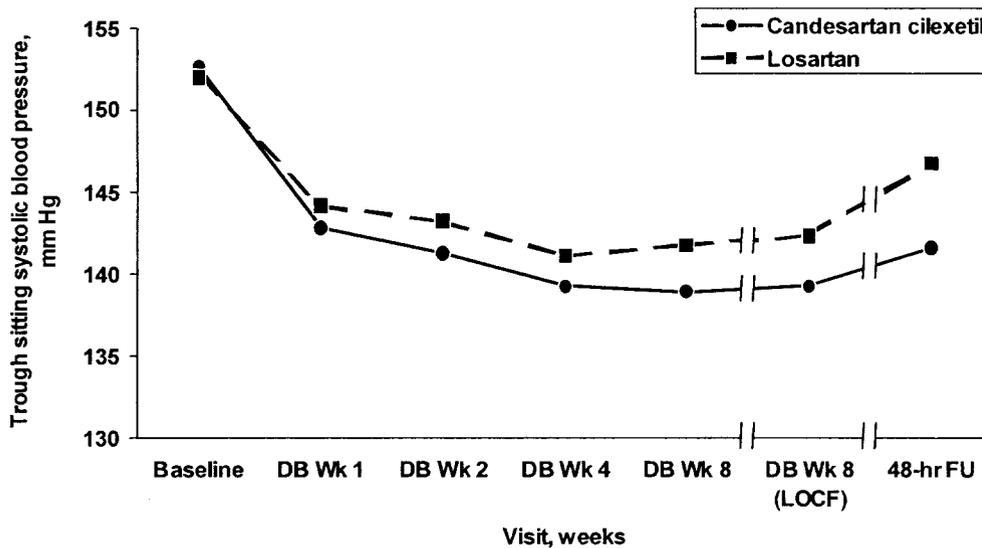


TABLE 6. Trough Sitting Systolic Blood Pressure (mm Hg) by Treatment and Visit (Study 231 ITT Population)

Treatment		Baseline	DB Wk 1	DB Wk 2*	DB Wk 4	DB Wk 8	DB Wk 8 (LOCF)	48-hr FU
Candesartan cilexetil	N	332	332	330	328	321	332	298
	Mean (SD)	152.6 (12.3)	142.8 (13.7)	141.2 (13.7)	139.2 (14.0)	138.9 (14.6)	139.2 (15.0)	141.6 (15.9)
Losartan	N	322	319	319	317	306	322	280
	Mean (SD)	152.0 (12.6)	144.2 (14.4)	143.2 (13.5)	141.1 (13.0)	141.7 (13.8)	142.3 (14.1)	146.7 (14.7)

*Doses were up-titrated at Week 2.

FIGURE 9.—Trough sitting systolic blood pressure (mm Hg) by treatment and visit (Study 231 ITT population).



Additional secondary efficacy measures (summarized in Table 2) demonstrated a significantly greater mean reduction in BP parameters for candesartan cilexetil compared with losartan. For both peak diastolic and systolic BP measures, candesartan cilexetil exhibited significantly greater reductions for the change from baseline to Week 8.

Trough to peak ratios (Table 7) exceeded 0.85 for both candesartan cilexetil and losartan in both studies, indicating the persistence of the blood pressure-lowering effect of both once-daily candesartan cilexetil and losartan for the full 24-hour (once-daily) dosing period.

TABLE 7. Trough to Peak Ratios for Sitting Diastolic Blood Pressure at Week 8 (Studies 230 and 231 ITT Population)

	Study 230	Study 231
Treatment	Trough to peak ratio	
Candesartan cilexetil	0.855	0.958
Losartan	0.915	0.877

In addition to differences in the extent of blood pressure-lowering, both studies demonstrated higher responder (Table 8) and controlled rates (Table 9) for the candesartan cilexetil group, although the differences were statistically significant ($p = 0.023$ for responders and $p = 0.033$ for controlled patients) only in Study 231. In Study 231, 207 (62.4%) of candesartan cilexetil-treated and 174 (54.0%) of losartan-treated patients were responders based on trough sitting diastolic BP (Table 8). In addition, 186 (56.0%) of candesartan cilexetil and 151 (46.9%) losartan patients were controlled based on trough sitting diastolic BP at Week 8 (Table 9).

TABLE 8. Number and Percentage of Responders Based on Trough Sitting Diastolic Blood Pressure at Double-blind Week 8 (Studies 230 and 231 ITT/LOCF Population)

	Study 230		Study 231	
	Candesartan cilexetil	Losartan	Candesartan cilexetil	Losartan
N	306	303	332	322
Number of responders	180	158	207	174
% Responders	58.8	52.1	62.4	54.0
Candesartan cilexetil vs losartan	p value = 0.103		p value = 0.033	

TABLE 9. Number and Percentage of Controlled Patients Based on Trough Sitting Diastolic Blood Pressure at Double-blind Week 8 (Studies 230 and 231 ITT/LOCF Population)

	Study 230		Study 231	
	Candesartan cilexetil	Losartan	Candesartan cilexetil	Losartan
N	306	303	332	322
Number controlled	150	135	186	151
% Controlled	49.0	44.6	56.0	46.9
Candesartan cilexetil vs losartan	p value = 0.291		p value = 0.023	

4.6.1 Efficacy in Subpopulations

Changes from baseline to Week 8 in diastolic and systolic BP across subpopulations based on age, gender, and race in studies 230 and 231 are summarized in Tables 10 and 11. The number of patients in some subpopulations was relatively small (age, ≥ 65 years; race, black), which necessitates caution in interpretation of these subset results. For example, in Study 230 the change from baseline in diastolic BP among black patients was slightly greater for losartan than for candesartan cilexetil, and the change from baseline among patients ≥ 65 years of age was the same for the two treatments. However in Study 231, the change from baseline to Week 8 in diastolic BP was greater with candesartan cilexetil treatment for both of these subgroups. In subgroups representing larger populations (non-black; age, < 65 years; females and males) trends in blood pressure-lowering effects of

candesartan cilexetil compared with losartan were consistent within studies, ie candesartan cilexetil exhibited greater mean reductions in diastolic and systolic BP. Overall, the trends for the comparative BP-reducing effects of candesartan cilexetil versus losartan on both diastolic and systolic BP for subpopulations based on age, race, and gender are consistent with the overall population results of the CLAIM program.

TABLE 10. Mean Change From Baseline to Week 8 (Observed) in Trough Sitting Diastolic Blood Pressure (mm Hg) by Treatment and Subpopulation (Studies 230 and 231 ITT Population)

Population	Study 230				Study 231			
	Candesartan cilexetil		Losartan		Candesartan cilexetil		Losartan	
	N	Change from baseline DBP	N	Change from baseline DBP	N	Change from baseline DBP	N	Change from baseline DBP
Overall	284	-10.4	280	-9.0	321	-11.0	306	-8.9
Black	57	-6.4	52	-7.7	57	-8.2	47	-6.6
Non-black	227	-11.4	228	-9.3	264	-11.6	259	-9.4
Age ≥ 65 years	58	-8.7	50	-8.7	52	-11.1	47	-8.1
Age < 65 years	226	-10.9	230	-9.1	269	-11.0	259	-9.1
Female	118	-11.1	121	-9.8	137	-11.3	127	-9.9
Male	166	-9.9	159	-8.4	184	-10.9	179	-8.3

TABLE 11. Mean Change From Baseline to Week 8 (Observed) in Trough Sitting Systolic Blood Pressure (mm Hg) by Treatment and Subpopulation (Studies 230 and 231 ITT Population)

Population	Study 230				Study 231			
	Candesartan cilexetil		Losartan		Candesartan cilexetil		Losartan	
	N	Change from baseline SBP	N	Change from baseline SBP	N	Change from baseline SBP	N	Change from baseline SBP
Overall	284	-13.7	280	-10.6	321	-13.7	306	-10.2
Black	57	-8.1	52	-8.4	57	-7.7	47	-5.4
Non-black	227	-15.2	228	-11.2	264	-15.0	259	-11.0
Age ≥ 65 years	58	-12.0	50	-9.5	52	-13.1	47	-9.0
Age < 65 years	226	-14.2	230	-10.9	269	-13.9	259	-10.4
Female	118	-15.4	121	-12.9	137	-15.0	127	-12.2
Male	166	-12.5	159	-9.0	184	-12.8	179	-8.7

4.6.2 Summary of Efficacy

These two studies provide a well-controlled, direct comparison between the BP-reducing effects of candesartan cilexetil and losartan in patients with hypertension. The data indicate a statistically significant difference in the primary efficacy measure (change in trough sitting diastolic BP at Week 8), demonstrating that candesartan cilexetil (16 mg QD forced-titrated at 2 weeks to 32 mg QD) is superior to losartan (50 mg QD forced-titrated at 2 weeks to 100 mg QD) in reducing trough sitting diastolic BP at 8 weeks. Furthermore, the greater blood pressure-lowering effect was consistent from Week 2 through the end of the study. Candesartan cilexetil was also superior to losartan for all secondary BP efficacy measures, including trough sitting systolic BP and peak blood pressures. The greater reduction in trough diastolic BP at 8 weeks with candesartan cilexetil was paralleled by higher rates of responders and controlled patients, although a statistically significant difference was only

observed in Study 231. Subgroup analysis also demonstrated consistent results across key populations based on gender, race and age. Overall, the data consistently support the conclusion that at the doses used in these studies, candesartan cilexetil provides superior blood pressure-lowering effects compared with losartan.

4.7 Summary of Safety and Tolerability

For all studies, safety measures included the incidence of treatment-emergent adverse events (AEs), serious adverse events (SAEs) and discontinuations due to AEs, physical examination findings, and clinical laboratory measurements. The safety population consisted of all randomized patients who had at least one post-baseline contact with a clinical study site.

A treatment-emergent AE was defined as: an event that started on or after entry into the double-blind portion of the study and did not occur during the placebo run-in period; an AE that occurred prior to entry into the double-blind portion of the study and increased in intensity after double-blind period entry; or any SAE that occurred after entry into the double-blind portion of the study.

Both candesartan cilexetil and losartan were well tolerated. The incidence of discontinuation for any reason for Studies 230 and 231 was 8.5% and 9.1% for candesartan cilexetil and losartan, respectively. The incidence of discontinuations due to adverse events was 2.7% and 1.8% for candesartan cilexetil and losartan, respectively. The adverse event profile of both drugs is consistent with their labeling.

4.7.1 Summary of Clinical Adverse Events

Treatment-emergent AEs occurring in at least 2% of patients (most common AEs) for Studies 230 and 231, as well as a pooled safety analysis of these two studies are summarized in Table 12. The pooled safety analysis demonstrated that the proportion of patients reporting an AE was similar in the candesartan cilexetil and losartan treatment groups. Treatment-emergent AEs were reported in 294 (46%) of 639 patients treated with candesartan cilexetil and 283 (45%) of 626 patients treated with losartan. Most treatment-emergent AEs were mild to moderate in severity, resolved with continued treatment, and did not appear related to study drug or drug dose administered (data not shown). Overall, there was no clinically meaningful consistent pattern to suggest there are any differences between treatments in safety and tolerability for these drugs. Adverse events were consistent with those described in the labeling for losartan (Cozaar®) and ATACAND®.

TABLE 12. Treatment-Emergent Adverse Events for Studies 230 and 231, Separate and Pooled, Occurring in at Least 2% of Patients

Treatment-emergent adverse events ^a	Study 230				Study 231				Pooled		Pooled	
	Candesartan cilexetil (n = 307)		Losartan (n = 304)		Candesartan cilexetil (n = 332)		Losartan (n = 322)		candesartan cilexetil (n = 639)		losartan (n = 626)	
	N	%	N	%	N	%	N	%	N	%	N	%
Any AE	140	45.6	136	44.7	154	46.4	147	45.7	294	46.0	283	45.2
Headache	22	7.2	18	5.9	15	4.5	17	5.3	37	5.8	35	5.6
Dizziness	11	3.6	4	1.3	17	5.1	8	2.5	28	4.4	12	1.9
Fatigue	5	1.6	11	3.6	6	1.8	4	1.2	11	1.7	15	2.4
Respiratory infection	12	3.9	24	7.9	30	9.0	32	9.9	42	6.6	56	8.9
Sinusitis	12	3.9	7	2.3	15	4.5	7	2.2	27	4.2	14	2.2
Rhinitis	2	0.7	11	3.6	10	3.0	9	2.8	12	1.9	20	3.2
Pharyngitis	5	1.6	4	1.3	4	1.2	12	3.7	9	1.4	16	2.6
Back pain	6	2.0	6	2.0	7	2.1	11	3.4	13	2.0	17	2.7
Edema peripheral	6	2.0	10	3.3	4	1.2	7	2.2	10	1.6	17	2.7

^aA treatment-emergent adverse event is an event starting on or after double-blind period entry that did not occur during the placebo run-in period, OR an adverse event that occurred prior to double-blind period entry that increased in intensity after double-blind period entry, OR any serious adverse event that occurred after double-blind period entry.

4.7.2 Serious Clinical Adverse Events

The pooled safety analysis demonstrated that the number of patients with SAEs was comparable in both treatment groups (Table 13). A total of ten SAEs in ten patients were reported, seven patients and three patients in the candesartan cilexetil and losartan treatment groups, respectively. None of the SAEs were considered related to study drug by investigator assessment, with the exception of one event of paroxysmal supraventricular tachycardia that occurred after 12 days of treatment with candesartan cilexetil. Candesartan cilexetil administration was discontinued, the patient was removed from the study, and the

tachycardia resolved. One cerebrovascular disorder event was considered possibly related to study treatment and occurred 8 days after the last dose of candesartan cilexetil. No deaths were reported in either Study 230 or Study 231.

TABLE 13. Serious Adverse Events (Studies 230 and 231)

Site/Patient ID/ Study No.	Treatment group	Preferred term	Relationship to study medication	Onset of AE: days from first dose*
022/002/230	Candesartan cilexetil	Paroxysmal supraventricular tachycardia	Probable	12
069/017/230	Candesartan cilexetil	Fracture Fracture Pneumothorax	Unlikely Unlikely Unlikely	72** 72** 72**
070/010/230	Candesartan cilexetil	Cerebrovascular disorder	Possible	65**
071/003/230	Candesartan cilexetil	Cerebrovascular disorder	Unlikely	42
055/013/230	Losartan	Fibrillation atrial	Unlikely	12
082/017/230	Losartan	Asthma aggravated Chronic obstruct airways disease	Unlikely Unlikely	51 51
235/003/231	Candesartan cilexetil	Cardiac failure	Unlikely	11
238/002/231	Candesartan cilexetil	Myocardial infarction	Unlikely	54
250/010/231	Candesartan cilexetil	Accident and/or Injury	Unlikely	48
257/016/231	Losartan	Colitis	Unlikely	36

*Days from first dose of double-blind medication.

**SAE occurred during 2-week safety follow-up at end of study. Last dose of study medication took place on Day 57 for both of these patients.

4.7.3 Discontinuations Due to Clinical Adverse Events

Overall, the discontinuation rate due to an AE was 2.7% (17 of 639 patients) for candesartan cilexetil and 1.8% (11 of 626 patients) for losartan. In Study 230, a total of 17 (2.8%) of 611 patients withdrew due to an AE; 11 (3.6%) in the candesartan cilexetil group and six (2.0%) in the losartan group. Table 14 presents the patients who withdrew due to a treatment-emergent adverse event along with the “blinded” causality assessment by the investigator.

TABLE 14. Adverse Events Leading to Discontinuation in Randomized Patients (Study 230)

Site/ Patient ID	Treatment	Adverse event (verbatim term)	Relationship to study medication	Onset of AE: days from first dose*
002/004	Candesartan cilexetil	Flatulence	Possible	12
003/005	Candesartan cilexetil	Stomach pain	Possible	46
012/004	Candesartan cilexetil	Worsening headache	Probable	15
		Hypotension	Probable	15
		Nausea	Probable	15
		Vomiting	Probable	15
022/002	Candesartan cilexetil	Hypotension	Probable	12
		Paroxysmal supraventricular tachycardia	Probable	12
025/018	Candesartan cilexetil	Severe headache	Possible	9
038/006	Candesartan cilexetil	Heart palpitations	Possible	21
		Intermittent vascular headaches	Possible	24
		Edema of hands	Possible	31
		Edema of lower extremities	Possible	31
063/003	Candesartan cilexetil	Right arm and hand numbness	Unlikely	2
		Right arm and hand tingles	Unlikely	2
069/017	Candesartan cilexetil	Fracture ribs	Unlikely	72**
		Fracture leg	Unlikely	72**
		Pneumothorax	Unlikely	72**
070/010	Candesartan cilexetil	(L) Cerebellar infarct	Possible	65**
071/003	Candesartan cilexetil	Stroke	Unlikely	42
077/007	Candesartan cilexetil	Tiredness	Possible	29
002/008	Losartan	Fatigue	Possible	15
008/004	Losartan	Mental agitate (agitation)	Possible	34
		Tired	Possible	34
		Vision blur (blurred)	Possible	34
023/003	Losartan	Epigastric burning	Possible	4
036/005	Losartan	Headache	Unlikely	36
055/013	Losartan	Congestive heart failure	Unlikely	10
		Pedal edema	Unlikely	12
		Rapid A-fib	Unlikely	12
063/004	Losartan	Hypotension	Possible	16

*Days from first dose of double-blind medication.

**AE occurred during 2-week safety follow-up at end of study. Last dose of study medication took place on Day 57 for both of these patients.

In Study 231, a total of 11 (1.7%) of 654 patients withdrew due to an AE: six (1.8%) in the candesartan cilexetil group and five (1.6%) in the losartan group (Table 15).

TABLE 15. Adverse Events Leading to Discontinuation in Randomized Patients (Study 231)

Site/Patient ID	Treatment	Adverse event (verbatim term)	Relationship to study medication	Onset of AE: days from first dose*
204/002	Candesartan ciloxetine	Chest pain (L) side	Possible	1
219/001	Candesartan ciloxetine	Problems with focusing eyes Confusion Dizziness Tingling LFT leg Fuzzy head	Possible Possible Possible Possible Probable	15 15 15 15 16
238/002	Candesartan ciloxetine	Myocardial infarction	Unlikely	54
238/006	Candesartan ciloxetine	Headache	Unlikely	21
249/006	Candesartan ciloxetine	Myocardial ischemia	Unlikely	1
250/002	Candesartan ciloxetine	Light-headedness Fatigue Diaphoresis	Possible Possible Possible	5 5 5
202/011	Losartan	Worsening headache	Unlikely	-7**
210/018	Losartan	Vertigo	Possible	15
215/008	Losartan	Abdominal cramps Back cramps (B) Hip cramps (B) Leg cramps Cloudy tympanic membrane	Possible Possible Possible Possible Unlikely	16 16 16 16 29
231/016	Losartan	CAD	Unlikely	33
240/008	Losartan	Lung congestion	Unlikely	12

*Days from first dose of double-blind medication.

**Please note that this AE began before the patient was randomized. However, the patient did discontinue from the study while in the double-blind portion of the study.

4.7.4 Summary of Laboratory Changes

Mean baseline and mean change from baseline at Week 8 laboratory measurements for key serum chemistry and hematologic parameters are summarized in Table 16. Overall, changes from baseline for all serum chemistry measurements were small and similar in magnitude across the two treatment groups in both studies. In addition, there were no clinically significant changes in mean laboratory values in either treatment group and there was no evidence suggesting an adverse effect on renal (serum potassium, sodium, serum creatinine, urea nitrogen), hepatic (ALAT, ASAT, alkaline phosphatase, total bilirubin), or metabolic function (blood glucose). Consistent with the uricosuric effect of losartan, a small decrease in serum uric acid (0.5 to 0.6 mg/dL) was evident in the two studies. There were no significant changes in hematologic measurements.

TABLE 16. Baseline Mean and Mean Change From Baseline for Serum Chemistry and Hematology Parameters in Randomized Patients in Studies 230 and 231

Parameter (Unit)	Study 230				Study 231			
	Candesartan cilexetil		Losartan		Candesartan cilexetil		Losartan	
	Baseline mean	Mean change	Baseline mean	Mean change	Baseline mean	Mean change	Baseline mean	Mean change
ALAT (U/L)	24.4	1.7	25.4	1.1	23.6	1.4	23.8	1.8
Alkaline phosphate (U/L)	76.3	0.4	77.2	3.1	76.3	0.5	74.4	2.3
ASAT (U/L)	20.9	1.1	21.4	-0.7	20.7	-0.7	20.8	0.1
Bilirubin, total (mg/dL)	0.6	0.0	0.6	0.0	0.6	0.0	0.6	0.0
Creatinine (mg/dL)	0.9	0.0	0.9	0.0	0.9	0.0	0.9	0.0
Potassium (mEq/L)	4.4	0.0	4.4	0.0	4.3	0.1	4.3	0.1
Urea nitrogen (mg/dL)	14.5	0.8	14.8	0.8	14.5	0.8	14.5	0.5
Uric acid (mg/dL)	5.6	-0.1	5.7	-0.6	5.6	0.0	5.6	-0.5
HCT (%)	42.9	-0.5	43.1	-0.3	42.6	-0.2	42.7	-0.2
Hb (g/dL)	14.4	-0.2	14.5	-0.1	14.4	-0.1	14.4	-0.1
WBC (10 ³ /μL)	6.4	-0.1	6.4	0.1	6.4	0.1	6.4	0.1

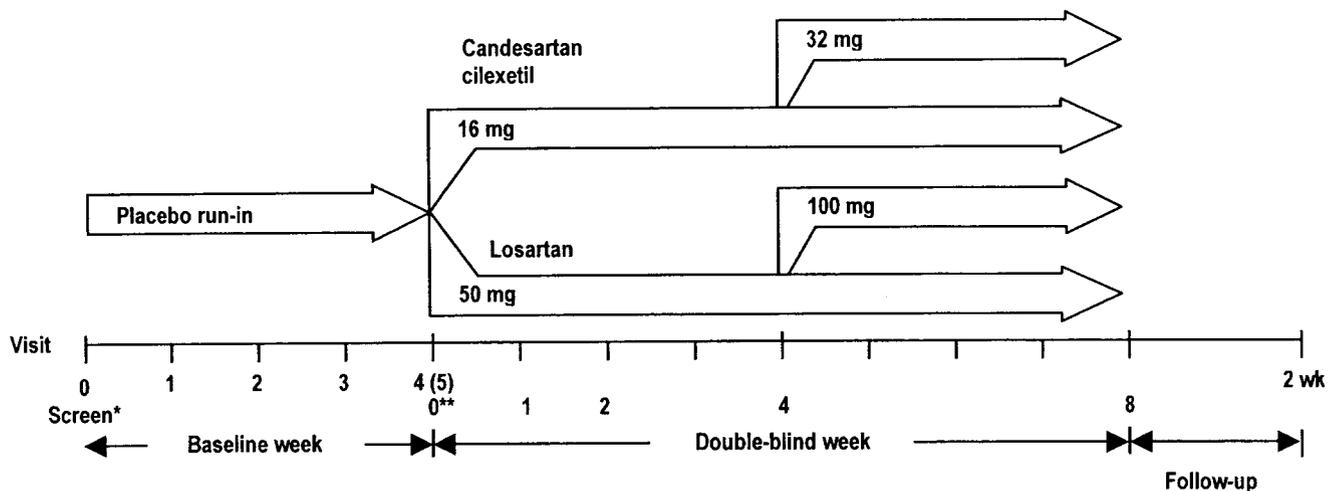
Overall, candesartan cilexetil and losartan were generally safe and well tolerated in the CLAIM studies. The incidence of treatment-emergent AEs was generally comparable between the two treatment groups. In addition, discontinuations due to AEs were comparable between candesartan cilexetil and losartan and there were no clinically significant changes in laboratory parameters. These studies are consistent with the labeling for both drugs.

5.0 SUPPORTIVE STUDIES

5.1 Summary of Study 175 (Candesartan vs. Losartan Evaluation, CANDLE)

Study 175 was an 8-week, multicenter, double-blind, randomized, titration-to-effect, parallel-group study designed to determine the efficacy, safety, and tolerability of candesartan cilexetil compared to losartan in hypertensive patients.^{13,18} A total of 332 patients with a sitting diastolic BP of 95 to 114 mm Hg during a placebo run-in period were randomized to receive either candesartan cilexetil 16 mg once daily or losartan 50 mg once daily (Figure 10). Patients with a mean sitting diastolic BP \geq 90 mm Hg after 4 weeks of treatment were up-titrated to candesartan cilexetil 32 mg or losartan 100 mg once daily for the remaining 4 weeks of study. Patients with a mean sitting diastolic BP $<$ 90 mm Hg after 4 weeks of treatment continued candesartan cilexetil 16 mg or losartan 50 mg once daily.

FIGURE 10.—Design of Study 175.

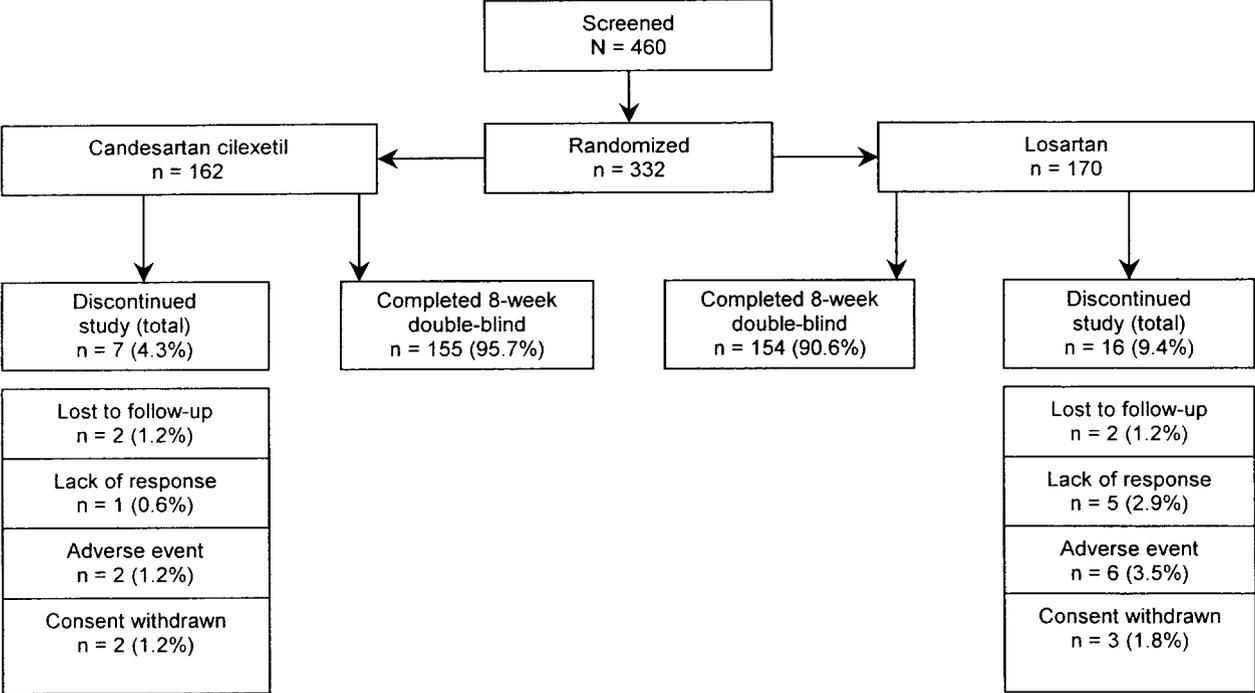


*Screen/baseline Week 0 visit allows for patients to be withdrawn from other antihypertensives prior to receiving study medication.

**Double-blind Week 0 = Qualifying/randomization visit (baseline Week 4 or optional baseline Week 5).

A total of 460 patients were screened at 41 clinical study sites and 332 were randomized. Of the 332 randomized patients, a total of 23 discontinued treatment during the double-blind portion of the study. A greater proportion (9.4%; n = 16) of patients discontinued treatment in the losartan group compared with the candesartan cilexetil group (4.3%; n = 7). The main reasons for discontinuations were adverse events or lack of efficacy. Overall, 309 (93.1%) randomized patients, 155 candesartan cilexetil-treated patients and 154 losartan-treated patients, completed the study (Figure 11).

FIGURE 11.—Disposition of patients in Study 175.



The primary antihypertensive efficacy measure was:

- Mean change in trough (24 ± 3 hours after dosing) sitting diastolic BP from baseline (end of the placebo run-in period/randomization visit) to the double-blind Week 8 visit

Secondary efficacy measures included:

- Mean change in trough sitting systolic BP
- Mean change in trough standing diastolic BP and systolic BP
- Mean change in peak (6 ± 2.5 hours after dosing) sitting and standing diastolic and systolic BP from baseline to Week 8
- Proportion of responders and controlled patients based on trough sitting diastolic BP at Week 8
 - Responders were defined as those patients with either a sitting diastolic BP of < 90 mm Hg or a decrease from baseline in trough sitting diastolic BP of ≥ 10 mm Hg
 - Controlled patients were defined as those patients with a sitting diastolic BP of < 90 mm Hg
- Trough to peak ratio for sitting diastolic BP at Week 8

This titration-to-effect study demonstrated that candesartan cilexetil, administered 16 mg once daily and titrated to 32 mg once daily after 4 weeks as required to control diastolic BP, was more effective in lowering trough sitting diastolic BP as compared to losartan 50 mg once daily titrated to 100 mg once daily after 4 weeks as required (mean difference, -2.2 mm Hg in favor of candesartan cilexetil; $p = 0.0158$). The candesartan cilexetil treatment regimen resulted in numerically greater reductions in every BP parameter measured compared with the losartan regimen. In addition, candesartan cilexetil treatment resulted in a higher percentage of responders (64% versus 54% for candesartan cilexetil and losartan,

respectively) and controlled patients (54% versus 43% for candesartan cilexetil and losartan, respectively). The trough to peak ratios for candesartan cilexetil and losartan (0.88 and 0.94, respectively) demonstrated the persistence of blood pressure-lowering of both regimens for a full 24 hours with once-daily dosing.

Both treatment regimens were safe and well tolerated with 1.2% (n = 2) candesartan cilexetil-treated and 3.5% (n = 6) losartan-treated patients withdrawing due to AEs. Eight patients reported a SAE, one (0.6%) treated with candesartan cilexetil and seven (4.1%) treated with losartan. There were no deaths reported and there were no clinically significant changes in laboratory values in either treatment group.

In summary, this study demonstrated that the candesartan cilexetil regimen was significantly ($p = 0.0158$) more effective than the losartan regimen in reducing trough sitting diastolic BP at Week 8 while maintaining an excellent safety and tolerability profile. In addition, candesartan cilexetil exhibited numerically greater reductions in secondary BP parameters, including sitting systolic BP and trough standing diastolic and systolic BP. Furthermore, the proportion of responders and controlled patients were higher with the candesartan cilexetil treatment regimen.

5.2 Summary of Other Related Clinical Study Information

5.2.1 Bioequivalence of Test Drug—Study SH-AHC-0015

AstraZeneca conducted Study SH-AHC-0015 to test the bioequivalence of the test drug used in Studies 230, 231, and 175. Study SH-AHC-0015 was an open-label, randomized, single-dose, two-way, crossover study that evaluated the bioequivalence between the standard tablets of losartan 50 mg and the standard tablets of losartan 50 mg of the same batch encapsulated in a gelatin capsule.¹⁹ Forty healthy volunteers participated in the study

and the two treatments periods were separated by a washout period of at least 6 days. The commercially available immediate-release tablets of losartan 50 mg or the encapsulated tablets of losartan 50 mg of the same batch were administered orally as a single dose with 240 mL of water. Plasma concentrations of losartan were determined immediately prior to and up to 36 hours after losartan administration in each period.

The least square estimates and 90% confidence intervals (CIs) for the ratio of true treatment medians, encapsulated/standard tablets, for losartan $AUC_{0-\infty}$ and for C_{max} were 1.00 (CI: 0.94,1.05) and 1.04 (CI: 0.93,1.17), respectively. The results indicate that the encapsulated tablet of losartan 50 mg is equivalent to the standard tablet of losartan 50 mg.

5.2.2 Study SH-AHM-0001

The efficacy and safety of candesartan cilexetil 8 mg and 16 mg once daily for 8 weeks was compared with losartan 50 mg once daily and placebo in a multicenter, randomized, double-blind, four-armed, parallel group study.¹⁵ Patients (20 to 80 years of age) with primary hypertension and a sitting diastolic BP of 95 to 114 mm Hg at Week -2 and Week 0 (during a 4-week, single-blind, placebo run-in period) were randomized to receive candesartan cilexetil 8 mg (n = 82), candesartan cilexetil 16 mg (n = 86), losartan 50 mg (n = 84), or placebo (n = 85) for 8 weeks. The primary efficacy variable was the change in trough (24-hour post-dose) sitting diastolic BP from baseline to Week 8 or the last value carried forward in the ITT population. In addition, peak (6 hours post-dose) sitting and standing BP and heart rate were measured at Weeks 0 and 8.

At baseline, mean sitting diastolic BP at trough for all treatment groups ranged between 101.7 and 103.5 mm Hg. Candesartan cilexetil at both dose levels (8 mg and 16 mg) had significant antihypertensive effects compared with placebo. Compared with placebo, trough

sitting diastolic BP was reduced by a mean of 8.9 mm Hg (95% CI: 6.0, 11.8) in the candesartan cilexetil 8-mg group and 10.3 mm Hg (95% CI: 7.4, 13.2) in the candesartan cilexetil 16-mg group. When compared with placebo, trough sitting systolic BP was reduced by a mean of 15.7 mm Hg (95% CI: 10.4, 21.0) in the candesartan cilexetil 8-mg group and 16.9 mm Hg (95% CI: 11.5, 22.2) in the candesartan cilexetil 16-mg group. Candesartan cilexetil 16 mg was significantly ($p = .013$) more effective than losartan 50 mg in reducing trough sitting diastolic BP by a mean difference of 3.7 mm Hg (95% CI; 0.8, 6.7).

The placebo-corrected trough-to-peak ratios (24 versus 6 hours post-dose) after treatment for 8 weeks with candesartan cilexetil were to 1.102 (8-mg dose) and 0.867 (16-mg dose) for sitting diastolic BP and 0.991 (8-mg dose) and 0.884 (16-mg dose) for sitting systolic BP. Due to a smaller effect on BP at trough, losartan treatment resulted in lower trough-to-peak ratios (0.723 for sitting diastolic BP and 0.719 for sitting systolic BP) compared with candesartan cilexetil treatment.

Half of the patients treated with candesartan cilexetil 8 mg and 57% of patients treated with candesartan cilexetil 16 mg were classified as responders (mean trough sitting diastolic BP ≤ 90 mm Hg and/or a reduction of ≥ 10 mm Hg) and almost 40% of patients (39.0% for 8-mg dose and 38.1% for 16-mg dose) were considered controlled (mean sitting diastolic BP ≤ 90 mm Hg). Only 15% and 7% of placebo-treated patients met the responder or controlled, criteria respectively. Both rates were significantly lower than observed in the two candesartan cilexetil treatment groups ($p < 0.001$). The percentages of responders and controlled patients were 50% and 39% in the 8-mg and 57% and 38% in the 16-mg candesartan cilexetil treatment groups compared with 46% and 29% in the losartan treatment group (not statistically different).

Both drugs were well tolerated. Eleven (11) patients withdrew from the study due to AEs (three in the placebo group, three in the candesartan cilexetil 8-mg group, one in the candesartan cilexetil 16-mg group, and four in the losartan group).

The results of this study were provided to the Division in the original NDA 20-838 and the study has also been published.¹⁵

6.0 SUMMARY OF OTHER PUBLISHED LITERATURE OF COMPARATOR TRIALS OF CANDESARTAN CILEXETIL AND LOSARTAN IN HYPERTENSIVE PATIENTS

The following three publications report on the findings of double-blind, randomized studies comparing the antihypertensive efficacy of candesartan cilexetil 16 mg and losartan 100 mg.

- Lacourcière Y, Asmar R. A comparison of the efficacy and duration of action of candesartan cilexetil and losartan as assessed by clinic and ambulatory blood pressure after a missed dose, in truly hypertensive patients: a placebo-controlled, forced titration study.¹⁴ Also published in Asmar R, Lacourcière Y. A new approach to assessing antihypertensive therapy: effect of treatment on pulse pressure. Candesartan cilexetil in Hypertension Ambulatory Measurement of Blood Pressure (CHAMP) Study Investigators.²⁰

This was a forced-titration study comparing candesartan cilexetil 16 mg with losartan 100 mg during the 24-hour dosing period as well as during the day when a missed dose occurred. Patients (n = 268) with sitting diastolic BP of 95 to 110 mm Hg and a mean awake ambulatory diastolic BP \geq 85 mm Hg were randomized to receive either candesartan cilexetil 8 mg, losartan 50 mg, or placebo once daily during an initial 4-week period. The doses were subsequently doubled (candesartan cilexetil to 16 mg; losartan to 100 mg) in all patients for an additional 4-week treatment period. Candesartan cilexetil once daily exhibited a significant dose-dependent reduction in ambulatory BP in doses ranging from 8 to 16 mg. Of key importance, candesartan cilexetil was more effective than losartan in reducing systolic ambulatory (during 36 hours after dosing) BP and in lowering both diastolic and systolic ambulatory BP on the day of a missed dose. Furthermore, both

regimens were safe and well tolerated with comparable clinical and laboratory safety assessments.¹⁴

- Mejia A, Jacovides A, Bernhardt DC, et al. Losartan and candesartan produce comparable blood pressure reductions but only losartan lowers plasma uric acid in hypertensive patients.²¹

This was a 12-week, titration-to-effect, comparative study of candesartan cilexetil 8 to 16 mg once daily and losartan 50 to 100 mg once daily. Patients (n = 929) with mild to moderate hypertension were randomized to receive losartan 50 mg or candesartan cilexetil 8 mg once daily for 6 weeks. The doses were then doubled if sitting diastolic BP remained > 90 mm Hg. Both treatment regimens lowered diastolic BP and systolic BP similarly and both regimens were safe and well tolerated. Serum uric acid levels were increased in the candesartan cilexetil group (0.13 mg/dL) whereas they were decreased in the losartan group (-0.14 mg/dL). However, the abstract did not discuss the statistical or clinical significance of the difference in uric acid levels between the two treatment groups.²¹

- Manolis AJ, Grossman E, Jelakovic B, et al. Effects of losartan and candesartan monotherapy and losartan/hydrochlorothiazide combination therapy in patients with mild to moderate hypertension. Losartan Trial Investigators.²²

This was a multicenter, double-blind, randomized, parallel-group study to compare the effects of losartan potassium, candesartan cilexetil, and losartan/hydrochlorothiazide (HCTZ) in patients with mild to moderate hypertension (sitting diastolic BP 95 to 115 mm

Hg. A total of 1,161 patients were randomized to 12 weeks of treatment with losartan 50 mg QD, possibly titrated to 100 mg QD (n = 461); candesartan cilexetil 8 mg QD, possibly titrated to 16 mg QD (n = 468); or losartan 50 mg QD, possibly titrated to losartan 50 mg plus HCTZ 12.5 mg QD (n = 232). At 6 weeks, the regimens of patients not reaching a goal SiDBP 90 mm Hg were titrated as described above, whereas patients achieving this goal continued with low-dose monotherapy. The single primary end point at 12 weeks tested the equivalence of the two monotherapy regimens, predefined as a maximum between-treatment difference in the mean change from baseline trough SiDBP of 2.5 mm Hg. The authors considered a ≥ 2.5 mm Hg difference in BP reduction clinically meaningful. At 12 weeks, changes in SiDBP/sitting and systolic blood pressure (SiSBP) of $-12.4/-14.4$ mm Hg with losartan 50 mg/100 mg Hg and $-13.1/-15.8$ mm Hg with candesartan cilexetil 8 mg/16 mg according to the authors, demonstrated equivalence between the two monotherapy regimens (95% CI for difference in SiDBP, -1.6 to 0.2 ; p-values for comparisons between candesartan cilexetil and losartan were not provided). At 12 weeks, the losartan 50 mg/50 mg plus HCTZ 12.5 mg regimen had reduced SiDBP/SiSBP significantly more ($-14.3/-18.0$ mm Hg) than either of the monotherapies for candesartan cilexetil 8 mg/16 mg (SiDBP, $p = 0.045$; SiSBP, $p = 0.017$) or losartan 50 mg/100 mg regimen (SiDBP, $p = 0.001$). Candesartan cilexetil 8 mg/16 mg increased serum uric acid levels (0.13 mg/dL; 95% CI, 0.04 to 0.23), whereas losartan 50 mg/100 mg decreased them (-0.14 mg/dL; 95% CI, -0.24 to -0.04), and losartan 50 mg/50 mg plus HCTZ 12.5 mg left them unchanged (0.06 mg/dL; 95% CI, -0.07 to 0.20). The authors concluded that losartan 50 mg/100 mg and candesartan cilexetil 8 mg/16 mg were comparable treatments in terms of blood pressure reduction. After titration, losartan 50 mg plus HCTZ 12.5 mg was superior to either candesartan cilexetil 16 mg or losartan 100 mg in reducing hypertension. This titration to effect study included 929 patients treated with candesartan cilexetil (n = 468) or losartan

monotherapy (n = 461). The results showed a numerically greater BP lowering effect of candesartan cilexetil 8 to 16 mg over losartan 50 to 100 mg with a good tolerability profile.

Overall, in the comparative efficacy studies, both candesartan cilexetil and losartan were safe and well tolerated, when used for the treatment of patients with hypertension. The AE profile for candesartan cilexetil in these studies is consistent with the profile described in the current product labeling.

7.0 DISCUSSION OF BENEFITS AND RISKS

Elevated BP increases the risk for catastrophic cardiovascular events (ie, stroke, heart attack, and cardiovascular death), as well as the cardiovascular risks associated with smoking and hypercholesterolemia.^{4,23} Although the Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of Hypertension (JNC VI) suggests a threshold for high-risk BP, there is a continuous, graded, direct relationship between BP, particularly systolic BP, and increased cardiovascular risk.⁴ The Multiple Risk Factor Intervention Trial (MRFIT) program found that over a 12-year period, men with systolic BP elevations of 20 mm Hg and 40 mm Hg experienced 156% and 244% higher risks for death due to coronary disease, respectively. This equates to a 6% to 8% increase in risk for every 1 mm Hg elevation in systolic BP.²³ Highest absolute risks occur in patients with additional risk factors such as hypercholesterolemia and smoking.^{23,24} Because of their high prevalence, even mild hypertension and “high normal” BP account for almost one third of the attributable risk for all cardiovascular disease.³

Importantly, incremental reduction in elevated BP effectively reduces the risk for cardiovascular events.²⁵⁻³⁰ The Systolic Hypertension in the Elderly Program (SHEP) demonstrated that treatment with diuretics with or without beta-blockers reduces systolic BP by approximately 11 to 14 mm Hg more than placebo, leading to reduced risks for myocardial infarction, heart failure, and stroke by 27%, 55%, and 37%, respectively.^{27,31} Across clinical trials there are differences in absolute cardiovascular risk reduction with drug therapy; however, proportionate reductions, which take into account event rates in placebo groups, are relatively constant. This implies a consistent effect of BP reduction on cardiovascular outcomes.³² Accordingly, drug-induced reductions³² in BP should lead to a predictable and continuous reduction in cardiovascular risk. This expectation is supported by

overview analyses of placebo-controlled trials that demonstrate a linear relationship between odds ratios for cardiovascular mortality and the active drug versus placebo difference in systolic BP.³³ For all cardiovascular events, the relationship is curvilinear.

Incremental reductions in BP imply a potential for major public health benefits. Over the period from 1976 to 1994, the rate of BP control among patients with hypertension in the United States increased from 10% to 27%, accounting for a substantial proportion of the reduction in cardiovascular morbidity and mortality rates. The reduction in stroke mortality in females > 50 years of age was striking: approximately 50% and 66% of the benefit in white and black females, respectively, was attributable to reduction in BP.⁴ Based on overview analyses of observational studies, MacMahon et al estimated that prolonged exposure to diastolic BP differing by 5, 7.5, and 10 mm Hg was associated with at least 34%, 46%, and 56% less stroke risk and 21%, 29%, and 37% less coronary heart disease risk, respectively.³⁴ Furthermore, Cook et al estimated that even a 2-mm Hg lower diastolic BP in a population that includes normotensive individuals would result in a 17% decrease in hypertension prevalence, a 6% reduction in coronary heart disease risk, and a 15% reduction in stroke risk.⁵ Systolic BP is also important. For example, Staessen and colleagues estimated that a modest (5 mm Hg) decrease in systolic BP with drug therapy accounts for a substantial portion of the therapeutic benefit in terms of fatal and nonfatal events prevented.³³

The studies in this submission demonstrate greater reductions in BP with candesartan cilexetil than with losartan when both agents are administered once daily at the maximum recommended total daily dose. The trough-to-peak diastolic BP ratios exceeded 0.85 for both drugs, demonstrating that, at the doses studied in these trials, a once-daily regimen is appropriate for both drugs. The finding of a greater BP reduction with candesartan cilexetil is

consistent with preclinical data that show a higher AT₁ receptor affinity, a greater angiotensin II blocking capability and a greater capacity for renin-angiotensin system (RAS) inhibition with candesartan.⁷

In the CLAIM studies, both drugs were well tolerated. Adverse events leading to study drug discontinuation were uncommon (2.7% and 1.8% for candesartan cilexetil and losartan, respectively). The rates and types of AEs were consistent with the well-characterized safety profile of the ARB class and with current approved labeling.

For antihypertensive drugs with similar safety and tolerability profiles, a modest advantage in BP reduction may contribute a meaningful therapeutic benefit to the population treated. The 3/2-mm Hg blood pressure reduction favoring candesartan cilexetil as observed in the CLAIM program represents a substantial fraction of the total placebo-corrected reduction in systolic BP/diastolic BP typically observed with losartan at doses of 50 to 100 mg (eg, 5.5 to 10.5 mm Hg/3.5 to 7.5 mm Hg) or with candesartan cilexetil at doses of 16 to 32 mg (eg, 8 to 12 mm Hg/4 to 8 mm Hg). For example, in the HOPE study of approximately 9,300 patients at high risk for cardiovascular events, a mean reduction in BP of 3.8/2.8 mm Hg in the ramipril-treated group versus 0.66/1.1 mm Hg in the placebo-treated group was observed.^{35,36} This placebo-corrected reduction in BP of approximately 3.1/1.7 mm Hg in the ramipril-treated group was associated with a 32% reduction in relative risk of stroke.³⁶

The CLAIM studies provide substantial evidence that candesartan cilexetil induces greater BP reduction than losartan in hypertensive patients when both agents are given once daily at their maximum recommended total daily dose. The magnitude of the blood pressure-lowering advantage for candesartan cilexetil is clinically meaningful and comes at no additional risk in terms of adverse safety or tolerability considerations. Furthermore, the

study findings can be generalized to a broad hypertensive population as only few categories of patients were excluded. The superior blood pressure lowering observed with the CLAIM studies is also consistent with other candesartan cilexetil versus losartan comparative studies using different dosing and study designs.

The addition of this clinically meaningful information to the label is important for the benefit of hypertensive patients and provides an enduring and convenient record for prescribers of prescription pharmaceuticals.

8.0 SUMMARY AND CONCLUSIONS

The conclusions that can be drawn from these studies and published literature include

- 1) Two identically designed, concurrently conducted 8-week, multicenter, double-blind, randomized, forced-dose–escalation studies demonstrated consistent, superior blood pressure-lowering with candesartan cilexetil compared to losartan at the maximum recommended doses administered once daily.
- 2) Candesartan cilexetil 32 mg once daily lowered trough, peak, and 48-hour post-dose diastolic and systolic BP more effectively than losartan 100 mg once daily in hypertensive patients in the United States.
- 3) Both drugs were well tolerated.
- 4) In addition, a titration-to-effect study supports that candesartan cilexetil 16 to 32 mg once daily is more effective in lowering trough sitting diastolic BP than losartan 50 to 100 mg once daily.
- 5) The greater blood pressure-lowering effect of candesartan cilexetil compared with losartan is consistent with preclinical and clinical pharmacology mechanistic data that predict greater antihypertensive benefit of candesartan cilexetil.
- 6) AstraZeneca believes that the substantial evidence of antihypertensive superiority of candesartan cilexetil over losartan presented in this supplement is clinically meaningful, provides important information to prescribers, and warrants inclusion in the label for ATACAND®.

9.0 PROPOSED LABELING

Clinical Trials subsection of CLINICAL PHARMACOLOGY:

“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 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. In these studies, both agents were well tolerated.”

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Appendix 1. Approved Labeling for ATACAND®

9174307
610002-07

ATACAND®
(*candesartan cilexetil*)

TABLETS

USE IN PREGNANCY

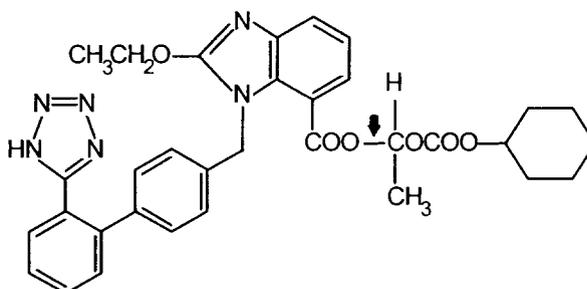
When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. When pregnancy is detected, ATACAND should be discontinued as soon as possible. See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

DESCRIPTION

ATACAND (*candesartan cilexetil*), a prodrug, is hydrolyzed to *candesartan* during absorption from the gastrointestinal tract. *Candesartan* is a selective AT₁ subtype angiotensin II receptor antagonist.

Candesartan cilexetil, a nonpeptide, is chemically described as (±)-1-[[[(cyclohexyloxy)carbonyl]oxy]ethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-benzimidazole-7-carboxylate.

Its empirical formula is C₃₃H₃₄N₆O₆, and its structural formula is



↓ site of ester hydrolysis.

Candesartan cilexetil is a white to off-white powder with a molecular weight of 610.67. It is practically insoluble in water and sparingly soluble in methanol. *Candesartan cilexetil* is a racemic mixture containing one chiral center at the cyclohexyloxycarbonyloxy ethyl ester group. Following oral administration, *candesartan cilexetil* undergoes hydrolysis at the ester link to form the active drug, *candesartan*, which is achiral.

ATACAND is available for oral use as tablets containing either 4 mg, 8 mg, 16 mg, or 32 mg of *candesartan cilexetil* and the following inactive ingredients: hydroxypropyl cellulose,

polyethylene glycol, lactose, corn starch, carboxymethylcellulose calcium, and magnesium stearate. Ferric oxide (reddish brown) is added to the 8-mg, 16-mg, and 32-mg tablets as a colorant.

CLINICAL PHARMACOLOGY

Mechanism of Action

Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin-converting enzyme (ACE, kininase II). Angiotensin II is the principal pressor agent of the renin-angiotensin system, with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation, and renal reabsorption of sodium. Candesartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT₁ receptor in many tissues, such as vascular smooth muscle and the adrenal gland. Its action is, therefore, independent of the pathways for angiotensin II synthesis.

There is also an AT₂ receptor found in many tissues, but AT₂ is not known to be associated with cardiovascular homeostasis. Candesartan has much greater affinity (>10,000-fold) for the AT₁ receptor than for the AT₂ receptor.

Blockade of the renin-angiotensin system with ACE inhibitors, which inhibit the biosynthesis of angiotensin II from angiotensin I, is widely used in the treatment of hypertension. ACE inhibitors also inhibit the degradation of bradykinin, a reaction also catalyzed by ACE. Because candesartan does not inhibit ACE (kininase II), it does not affect the response to bradykinin. Whether this difference has clinical relevance is not yet known. Candesartan does not bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

Blockade of the angiotensin II receptor inhibits the negative regulatory feedback of angiotensin II on renin secretion, but the resulting increased plasma renin activity and angiotensin II circulating levels do not overcome the effect of candesartan on blood pressure.

Pharmacokinetics

General

Candesartan cilexetil is rapidly and completely bioactivated by ester hydrolysis during absorption from the gastrointestinal tract to candesartan, a selective AT₁ subtype angiotensin II receptor antagonist. Candesartan is mainly excreted unchanged in urine and feces (via bile). It undergoes minor hepatic metabolism by O-deethylation to an inactive metabolite. The elimination half-life of candesartan is approximately 9 hours. After single and repeated administration, the pharmacokinetics of candesartan are linear for oral doses up to 32 mg of candesartan cilexetil. Candesartan and its inactive metabolite do not accumulate in serum upon repeated once-daily dosing.

Following administration of candesartan cilexetil, the absolute bioavailability of candesartan was estimated to be 15%. After tablet ingestion, the peak serum concentration (C_{max}) is reached after 3 to 4 hours. Food with a high fat content does not affect the bioavailability of candesartan after candesartan cilexetil administration.

Metabolism and Excretion

Total plasma clearance of candesartan is 0.37 mL/min/kg, with a renal clearance of 0.19 mL/min/kg. When candesartan is administered orally, about 26% of the dose is excreted unchanged in urine. Following an oral dose of ¹⁴C-labeled candesartan cilexetil, approximately 33% of radioactivity is recovered in urine and approximately 67% in feces. Following an intravenous dose of ¹⁴C-labeled candesartan, approximately 59% of radioactivity is recovered in urine and approximately 36% in feces. Biliary excretion contributes to the elimination of candesartan.

Distribution

The volume of distribution of candesartan is 0.13 L/kg. Candesartan is highly bound to plasma proteins (>99%) and does not penetrate red blood cells. The protein binding is constant at candesartan plasma concentrations well above the range achieved with recommended doses. In rats, it has been demonstrated that candesartan crosses the blood-brain barrier poorly, if at all. It has also been demonstrated in rats that candesartan passes across the placental barrier and is distributed in the fetus.

Special Populations

Pediatric— The pharmacokinetics of candesartan cilexetil have not been investigated in patients <18 years of age.

Geriatric and Gender— The pharmacokinetics of candesartan have been studied in the elderly (≥65 years) and in both sexes. The plasma concentration of candesartan was higher in the elderly (C_{max} was approximately 50% higher, and AUC was approximately 80% higher) compared to younger subjects administered the same dose. The pharmacokinetics of candesartan were linear in the elderly, and candesartan and its inactive metabolite did not accumulate in the serum of these subjects upon repeated, once-daily administration. No initial dosage adjustment is necessary. (See DOSAGE AND ADMINISTRATION.) There is no difference in the pharmacokinetics of candesartan between male and female subjects.

Renal Insufficiency— In hypertensive patients with renal insufficiency, serum concentrations of candesartan were elevated. After repeated dosing, the AUC and C_{max} were approximately doubled in patients with severe renal impairment (creatinine clearance <30 mL/min/1.73m²) compared to patients with normal kidney function. The pharmacokinetics of candesartan in hypertensive patients undergoing hemodialysis are similar to those in hypertensive patients with severe renal impairment. Candesartan cannot be removed by hemodialysis. No initial dosage adjustment is necessary in patients with renal insufficiency. (See DOSAGE AND ADMINISTRATION.)

Hepatic Insufficiency— No differences in the pharmacokinetics of candesartan were observed in patients with mild to moderate chronic liver disease. The pharmacokinetics after candesartan cilexetil administration have not been investigated in patients with severe hepatic insufficiency. No initial dosage adjustment is necessary in patients with mild hepatic disease. (See DOSAGE AND ADMINISTRATION.)

Drug Interactions

See PRECAUTIONS, Drug Interactions.

Pharmacodynamics

Candesartan inhibits the pressor effects of angiotensin II infusion in a dose-dependent manner. After 1 week of once-daily dosing with 8 mg of candesartan cilexetil, the pressor effect was inhibited by approximately 90% at peak with approximately 50% inhibition persisting for 24 hours.

Plasma concentrations of angiotensin I and angiotensin II, and plasma renin activity (PRA), increased in a dose-dependent manner after single and repeated administration of candesartan cilexetil to healthy subjects and hypertensive patients. ACE activity was not altered in healthy subjects after repeated candesartan cilexetil administration. The once-daily administration of up to 16 mg of candesartan cilexetil to healthy subjects did not influence plasma aldosterone concentrations, but a decrease in the plasma concentration of aldosterone was observed when 32 mg of candesartan cilexetil was administered to hypertensive patients. In spite of the effect of candesartan cilexetil on aldosterone secretion, very little effect on serum potassium was observed.

In multiple-dose studies with hypertensive patients, there were no clinically significant changes in metabolic function, including serum levels of total cholesterol, triglycerides, glucose, or uric acid. In a 12-week study of 161 patients with non-insulin-dependent (type 2) diabetes mellitus and hypertension, there was no change in the level of HbA_{1c}.

Clinical Trials

The antihypertensive effects of ATACAND were examined in 14 placebo-controlled trials of 4- to 12-weeks duration, primarily at daily doses of 2 to 32 mg per day in patients with baseline diastolic blood pressures of 95 to 114 mm Hg. Most of the trials were of candesartan cilexetil as a single agent, but it was also studied as add-on to hydrochlorothiazide and amlodipine. These studies included a total of 2350 patients randomized to one of several doses of candesartan cilexetil and 1027 to placebo. Except for a study in diabetics, all studies showed significant effects, generally dose related, of 2 to 32 mg on trough (24 hour) systolic and diastolic pressures compared to placebo, with doses of 8 to 32 mg giving effects of about 8-12/4-8 mm Hg. There were no exaggerated first-dose effects in these patients. Most of the antihypertensive effect was seen within 2 weeks of initial dosing and the full effect in 4 weeks. With once-daily dosing, blood pressure effect was maintained over 24 hours, with trough-to-peak ratios of blood pressure effect generally over 80%. Candesartan cilexetil had an additional blood pressure lowering effect when added to hydrochlorothiazide.

The antihypertensive effect was similar in men and women and in patients older and younger than 65. Candesartan was effective in reducing blood pressure regardless of race, although the effect was somewhat less in blacks (usually a low-renin population). This has been generally true for angiotensin II antagonists and ACE inhibitors.

In long-term studies of up to 1 year, the antihypertensive effectiveness of candesartan cilexetil was maintained, and there was no rebound after abrupt withdrawal.

There were no changes in the heart rate of patients treated with candesartan cilexetil in controlled trials.

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

ATACAND is contraindicated in patients who are hypersensitive to any component of this product.

WARNINGS

Fetal/Neonatal Morbidity and Mortality

Drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature in patients who were taking angiotensin-converting enzyme inhibitors. When pregnancy is detected, ATACAND should be discontinued as soon as possible.

The use of drugs that act directly on the renin-angiotensin system during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to exposure to the drug.

These adverse effects do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to an angiotensin II receptor antagonist only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should have the patient discontinue the use of ATACAND as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to a drug acting on the renin-angiotensin system will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intra-amniotic environment.

If oligohydramnios is observed, ATACAND should be discontinued unless it is considered life saving for the mother. Contraction stress testing (CST), a nonstress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to an angiotensin II receptor antagonist should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function.

There is no clinical experience with the use of ATACAND in pregnant women. Oral doses \geq 10 mg of candesartan cilexetil/kg/day administered to pregnant rats during late gestation and continued through lactation were associated with reduced survival and an increased incidence of hydronephrosis in the offspring. The 10-mg/kg/day dose in rats is approximately 2.8 times the maximum recommended daily human dose (MRHD) of 32 mg on a mg/m² basis (comparison assumes human body weight of 50 kg). Candesartan cilexetil given to

pregnant rabbits at an oral dose of 3 mg/kg/day (approximately 1.7 times the MRHD on a mg/m² basis) caused maternal toxicity (decreased body weight and death) but, in surviving dams, had no adverse effects on fetal survival, fetal weight, or external, visceral, or skeletal development. No maternal toxicity or adverse effects on fetal development were observed when oral doses up to 1000 mg of candesartan cilexetil/kg/day (approximately 138 times the MRHD on a mg/m² basis) were administered to pregnant mice.

Hypotension in Volume- and Salt-Depleted Patients

In patients with an activated renin-angiotensin system, such as volume- and/or salt-depleted patients (eg, those being treated with diuretics), symptomatic hypotension may occur. These conditions should be corrected prior to administration of ATACAND, or the treatment should start under close medical supervision (see DOSAGE AND ADMINISTRATION).

If hypotension occurs, the patients should be placed in the supine position and, if necessary, given an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further treatment which usually can be continued without difficulty once the blood pressure has stabilized.

PRECAUTIONS

General

Impaired Renal Function— As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals treated with ATACAND. In patients whose renal function may depend upon the activity of the renin-angiotensin-aldosterone system (eg, patients with severe congestive heart failure), treatment with angiotensin-converting enzyme inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. Similar results may be anticipated in patients treated with ATACAND. (See CLINICAL PHARMACOLOGY, Special Populations.)

In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen (BUN) have been reported. There has been no long-term use of ATACAND in patients with unilateral or bilateral renal artery stenosis, but similar results may be expected.

Information for Patients

Pregnancy— Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to drugs that act on the renin-angiotensin system, and they should also be told that these consequences do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

Drug Interactions

No significant drug interactions have been reported in studies of candesartan cilexetil given with other drugs such as glyburide, nifedipine, digoxin, warfarin, hydrochlorothiazide, and oral contraceptives in healthy volunteers. Because candesartan is not significantly metabolized by the cytochrome P450 system and at therapeutic concentrations has no effects on P450 enzymes, interactions with drugs that inhibit or are metabolized by those enzymes would not be expected.

Carcinogenesis, Mutagenesis, Impairment of Fertility

There was no evidence of carcinogenicity when candesartan cilexetil was orally administered to mice and rats for up to 104 weeks at doses up to 100 and 1000 mg/kg/day, respectively. Rats received the drug by gavage, whereas mice received the drug by dietary administration. These (maximally-tolerated) doses of candesartan cilexetil provided systemic exposures to candesartan (AUCs) that were, in mice, approximately 7 times and, in rats, more than 70 times the exposure in man at the maximum recommended daily human dose (32 mg).

Candesartan cilexetil was not genotoxic in the microbial mutagenesis and mammalian cell mutagenesis assays and in the *in vivo* chromosomal aberration and rat unscheduled DNA synthesis assays. In addition, candesartan was not genotoxic in the microbial mutagenesis, mammalian cell mutagenesis, and *in vitro* and *in vivo* chromosome aberration assays.

Fertility and reproductive performance were not affected in studies with male and female rats given oral doses of up to 300 mg/kg/day (83times the maximum daily human dose of 32 mg on a body surface area basis).

Pregnancy

Pregnancy Categories C (first trimester) and *D* (second and third trimesters). See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

Nursing Mothers

It is not known whether candesartan is excreted in human milk, but candesartan has been shown to be present in rat milk. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Of the total number of subjects in clinical studies of ATACAND, 21% were 65 and over, while 3% were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. In a placebo-controlled trial of about 200 elderly hypertensive patients (ages 65 to 87 years), administration of candesartan cilexetil was well tolerated and lowered blood pressure by about 12/6 mm Hg more than placebo.

ADVERSE REACTIONS

ATACAND has been evaluated for safety in more than 3600 patients/subjects, including more than 3200 patients treated for hypertension. About 600 of these patients were studied for at least 6 months and about 200 for at least 1 year. In general, treatment with ATACAND was well tolerated. The overall incidence of adverse events reported with ATACAND was similar to placebo.

The rate of withdrawals due to adverse events in all trials in patients (7510 total) was 3.3% (ie, 108 of 3260) of patients treated with candesartan cilexetil as monotherapy and 3.5% (ie,

39 of 1106) of patients treated with placebo. In placebo-controlled trials, discontinuation of therapy due to clinical adverse events occurred in 2.4% (ie, 57 of 2350) of patients treated with ATACAND and 3.4% (ie, 35 of 1027) of patients treated with placebo.

The most common reasons for discontinuation of therapy with ATACAND were headache (0.6%) and dizziness (0.3%).

The adverse events that occurred in placebo-controlled clinical trials in at least 1% of patients treated with ATACAND and at a higher incidence in candesartan cilexetil (n = 2350) than placebo (n = 1027) patients included back pain (3% vs 2%), dizziness (4% vs 3%), upper respiratory tract infection (6% vs 4%), pharyngitis (2% vs 1%), and rhinitis (2% vs 1%).

The following adverse events occurred in placebo-controlled clinical trials at a more than 1% rate but at about the same or greater incidence in patients receiving placebo compared to candesartan cilexetil: fatigue, peripheral edema, chest pain, headache, bronchitis, coughing, sinusitis, nausea, abdominal pain, diarrhea, vomiting, arthralgia, albuminuria.

Other potentially important adverse events that have been reported, whether or not attributed to treatment, with an incidence of 0.5% or greater from the more than 3200 patients worldwide treated with ATACAND are listed below. It cannot be determined whether these events were causally related to ATACAND. **Body as a Whole:** asthenia, fever; **Central and Peripheral Nervous System:** paresthesia, vertigo; **Gastrointestinal System Disorder:** dyspepsia, gastroenteritis; **Heart Rate and Rhythm Disorders:** tachycardia, palpitation; **Metabolic and Nutritional Disorders:** creatine phosphokinase increased, hyperglycemia, hypertriglyceridemia, hyperuricemia; **Musculoskeletal System Disorders:** myalgia; **Platelet/Bleeding-Clotting Disorders:** epistaxis; **Psychiatric Disorders:** anxiety, depression, somnolence; **Respiratory System Disorders:** dyspnea; **Skin and Appendages Disorders:** rash, sweating increased; **Urinary System Disorders:** hematuria.

Other reported events seen less frequently included angina pectoris, myocardial infarction, and angioedema.

Adverse events occurred at about the same rates in men and women, older and younger patients, and black and nonblack patients.

Post-Marketing Experience

The following have been very rarely reported in post-marketing experience:

Digestive: Abnormal hepatic function and hepatitis.

Hematologic: Neutropenia, leukopenia, and agranulocytosis.

Skin and Appendages Disorders: Pruritus and urticaria.

Laboratory Test Findings

In controlled clinical trials, clinically important changes in standard laboratory parameters were rarely associated with the administration of ATACAND.

Creatinine, Blood Urea Nitrogen— Minor increases in blood urea nitrogen (BUN) and serum creatinine were observed infrequently.

Hyperuricemia— Hyperuricemia was rarely found (19 or 0.6% of 3260 patients treated with candesartan cilexetil and 5 or 0.5% of 1106 patients treated with placebo).

Hemoglobin and Hematocrit— Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.2 grams/dL and 0.5 volume percent, respectively) were observed in patients treated with ATACAND alone but were rarely of clinical importance. Anemia, leukopenia, and thrombocytopenia were associated with withdrawal of one patient each from clinical trials.

Potassium— A small increase (mean increase of 0.1 mEq/L) was observed in patients treated with ATACAND alone but was rarely of clinical importance. One patient from a congestive heart failure trial was withdrawn for hyperkalemia (serum potassium = 7.5 mEq/L). This patient was also receiving spironolactone.

Liver Function Tests— Elevations of liver enzymes and/or serum bilirubin were observed infrequently. Five patients assigned to candesartan cilexetil in clinical trials were withdrawn because of abnormal liver chemistries. All had elevated transaminases. Two had mildly elevated total bilirubin, but one of these patients was diagnosed with Hepatitis A.

OVERDOSAGE

No lethality was observed in acute toxicity studies in mice, rats, and dogs given single oral doses of up to 2000 mg/kg of candesartan cilexetil. In mice given single oral doses of the primary metabolite, candesartan, the minimum lethal dose was greater than 1000 mg/kg but less than 2000 mg/kg.

Limited data are available in regard to overdosage in humans. In one recorded case of an intentional overdose, a 43-year-old female patient (Body Mass Index of 31 kg/m²) ingested an estimated 160 mg of candesartan cilexetil in conjunction with multiple other pharmaceutical agents (ibuprofen, naproxen sodium, diphenhydramine hydrochloride, and ketoprofen). Gastric lavage was performed; the patient was monitored in hospital for several days and was discharged without sequelae.

Candesartan cannot be removed by hemodialysis.

Treatment: To obtain up-to-date information about the treatment of overdose, consult your Regional Poison Control Center. Telephone numbers of certified poison control centers are listed in the *Physicians' Desk Reference (PDR)*. In managing overdose, consider the possibilities of multiple-drug overdoses, drug-drug interactions, and altered pharmacokinetics in your patient.

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

DOSAGE AND ADMINISTRATION

Dosage must be individualized. Blood pressure response is dose related over the range of 2 to 32 mg. The usual recommended 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.

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). For patients with possible depletion of intravascular volume (eg, 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 in Volume- and Salt-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.

HOW SUPPLIED

No. 3782 — Tablets ATACAND, 4 mg, are white to off-white, circular/biconvex-shaped, non-film-coated tablets, coded ACF on one side and 004 on the other. They are supplied as follows:

NDC 0186-0004-31 unit of use bottles of 30.

No. 3780 — Tablets ATACAND, 8 mg, are light pink, circular/biconvex-shaped, non-film-coated tablets, coded ACG on one side and 008 on the other. They are supplied as follows:

NDC 0186-0008-31 unit of use bottles of 30.

No. 3781 — Tablets ATACAND, 16 mg, are pink, circular/biconvex-shaped, non-film-coated tablets, coded ACH on one side and 016 on the other. They are supplied as follows:

NDC 0186-0016-31 unit of use bottles of 30

NDC 0186-0016-54 unit of use bottles of 90

NDC 0186-0016-28 unit dose packages of 100.

No. 3791 — Tablets ATACAND, 32 mg, are pink, circular/biconvex-shaped, non-film-coated tablets, coded ACL on one side and 032 on the other. They are supplied as follows:

NDC 0186-0032-31 unit of use bottles of 30

NDC 0186-0032-54 unit of use bottles of 90

NDC 0186-0032-28 unit dose packages of 100.

Storage

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Keep container tightly closed.

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from Takeda Chemical Industries, Ltd.
by: AstraZeneca AB, S-151 85 Södertälje, Sweden
for: AstraZeneca LP, Wilmington, DE 19850

Made in Sweden

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Appendix 2. Tabular Summary of Comparator Labeling

Product	Date of approval	Summary of Comparator Information	Date of Label
Zestril® / Prinvil® (lisinopril)	12/87	<p>CLINICAL PHARMACOLOGY, Pharmacodynamics and Clinical Effects, Hypertension – 6th paragraph</p> <p>...In controlled clinical studies, Zestril 20-80 mg has been compared in patients with mild to moderate hypertension to hydrochlorothiazide 12.5-50 mg and with atenolol 50-200 mg; and in patients with moderate to severe hypertension to metoprolol 100-200 mg. It was superior to hydrochlorothiazide in effects on systolic and diastolic pressure in a population that was ¾ Caucasian. Zestril was approximately equivalent to atenolol and metoprolol in effects on diastolic blood pressure, and had somewhat greater effects on systolic blood pressure.</p>	Jan-02

Product	Date of approval	Summary of Comparator Information	Date of Label																
Cozaar® (losartan potassium)	4/95	<p data-bbox="378 942 412 1423">Adverse Reactions – 9th paragraph</p> <p data-bbox="448 384 789 1423">Persistent dry cough (with an incidence of a few percent) has been associated with ACE inhibitor use and in practice can be a cause of discontinuation of ACE inhibitor therapy. Two prospective, parallel-group, double-blind, randomized, controlled trials were conducted to assess the effects of losartan on the incidence of cough in hypertensive patients who had experienced cough while receiving ACE inhibitor therapy. Patients who had typical ACE inhibitor cough when challenged with lisinopril, whose cough disappeared on placebo, were randomized to losartan 50 mg, lisinopril 20 mg, or either placebo (one study, n=97) or 25 mg hydrochlorothiazide (n=135). The double-blind treatment period lasted up to 8 weeks. The incidence of cough is shown below.</p> <table data-bbox="824 573 1036 1423"> <tr> <td data-bbox="824 1287 859 1398">Study 1[†]</td> <td data-bbox="824 1119 859 1203">HCTZ</td> <td data-bbox="824 867 859 993">Losartan</td> <td data-bbox="824 615 859 741">Lisinopril</td> </tr> <tr> <td data-bbox="902 1287 937 1398">Cough</td> <td data-bbox="902 1119 937 1203">25%</td> <td data-bbox="902 867 937 993">17%</td> <td data-bbox="902 615 937 741">69%</td> </tr> <tr> <td data-bbox="980 1287 1015 1398">Study 2^{††}</td> <td data-bbox="980 1119 1015 1203">Placebo</td> <td data-bbox="980 867 1015 993">Losartan</td> <td data-bbox="980 615 1015 741">Lisinopril</td> </tr> <tr> <td data-bbox="1058 1287 1092 1398">Cough</td> <td data-bbox="1058 1119 1092 1203">35%</td> <td data-bbox="1058 867 1092 993">29%</td> <td data-bbox="1058 615 1092 741">62%</td> </tr> </table> <p data-bbox="1128 667 1149 1077">† Demographics = (89% Caucasian, 64% female)</p> <p data-bbox="1174 667 1195 1077">†† Demographics = (90% Caucasian, 51% female)</p> <p data-bbox="1222 384 1317 1423">These studies demonstrate that the incidence of cough associated with losartan therapy, in a population that all had cough associated with ACE inhibitor therapy, is similar to that associated with hydrochlorothiazide or placebo therapy.</p>	Study 1 [†]	HCTZ	Losartan	Lisinopril	Cough	25%	17%	69%	Study 2 ^{††}	Placebo	Losartan	Lisinopril	Cough	35%	29%	62%	Nov-01
Study 1 [†]	HCTZ	Losartan	Lisinopril																
Cough	25%	17%	69%																
Study 2 ^{††}	Placebo	Losartan	Lisinopril																
Cough	35%	29%	62%																

Product	Date of approval	Summary of Comparator Information	Date of Label
Accupril® (quinapril hydrochloride tablets)	11/91	<p data-bbox="412 394 488 1423">CLINICAL PHARMACOLOGY, Pharmacodynamics and Clinical Effects – 5th paragraph</p> <p data-bbox="516 407 586 1423">In patients with hypertension, Accupril 10-40 mg was similar in effectiveness to captopril, enalapril, propranolol, and thiazide diuretics.</p>	Mar-01
Altace® Capsules (ramipril)	1/91	<p data-bbox="656 449 725 1423">CLINICAL PHARMACOLOGY, Pharmacodynamics and Clinical Effects, Hypertension – 4th paragraph</p> <p data-bbox="758 386 894 1423">Altace has been compared with other ACE inhibitors, beta-blockers, and thiazide diuretics. It was approximately as effective as other ACE inhibitors and as atenolol. In both Caucasians and blacks, hydrochlorothiazide (25 or 50 mg) was significantly more effective than ramipril.</p>	Nov-01
Diovan® (valsartan)	12/96	<p data-bbox="964 428 1034 1423">CLINICAL PHARMACOLOGY, Pharmacodynamics and Clinical Effects – 13th paragraph</p> <p data-bbox="1066 407 1131 1423">In controlled trials, the antihypertensive effect of once-daily Diovan 80 mg was similar to that of once-daily enalapril 20 mg or once-daily lisinopril 10 mg.</p>	Jun-01

Product	Date of approval	Summary of Comparator Information	Date of Label
Teveten® (eprosartan mesylate)	12/97	<p data-bbox="380 596 412 1411">CLINICAL PHARMACOLOGY, Clinical Trials – 6th paragraph</p> <p data-bbox="451 386 896 1411">Angiotensin-converting enzyme (ACE) inhibitor-induced cough (a dry, persistent cough) can lead to discontinuation of ACE inhibitor therapy. In one study, patients who had previously coughed while taking an ACE inhibitor were treated with eprosartan, an ACE inhibitor (enalapril) or placebo for six weeks. The incidence of dry, persistent cough was 2.2% on eprosartan, 4.4% on placebo, and 20.5% on the ACE inhibitor; p=0.008 for the comparison of eprosartan with enalapril. In a second study comparing the incidence of cough in 259 patients treated with eprosartan to 261 patients treated with the ACE inhibitor enalapril, the incidence of dry, persistent cough in eprosartan-treated patients (1.5%) was significantly lower (p=0.018) than that observed in patients treated with the ACE inhibitor (5.4%). In addition, analysis of overall data from six double-blind clinical trials involving 1,554 patients showed an incidence of spontaneously reported cough in patients treated with eprosartan of 3.5%, similar to placebo (2.6%).</p>	Sep-00