

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER**

**20-838/S-015**

**Medical Review(s)**



Douglas C. Throckmorton, M.D.  
Division of Cardio-Renal Drug Products, HFD-110

Food and Drug Administration  
5600 Fishers Lane  
Rockville, MD 20857  
Tel (301) 594-5365, FAX (301) 594-5494

### Memorandum

**DATE:** 7.24.02

**FROM:** Douglas C. Throckmorton, M.D., Director  
Division of Cardio-Renal Drug Products (DCRDP), HFD-110

**SUBJECT:** NDA 20-838/S015,  
**NAME OF DRUG:** Candesartan Cilexetil  
**SPONSOR:** AstraZeneca LP

#### DOCUMENTS USED FOR MEMO:

1. Pharmacology Toxicology review by Anthony G. Proakis, Ph.D., dated 4.29.02

#### CONCLUSIONS

This memorandum corrects an omission in my recent Divisional memorandum concerning the approvability of candesartan as superior to losartan. In that memorandum I failed to take note of a Pharmacology-Toxicology review by Dr. Proakis. His review, while not strictly related to the superiority claim, relates to some change in the description for the genotoxicity labeling and his proposed text is included in the proposed labeling changes.

#### BACKGROUND

As a part of the review of the label, Dr. Proakis noted that the interpretation of two genotoxicity tests conducted on the *parent compound* and on its O-deethyl metabolite of candesartan did not conform to current ICH guidelines (see his review for details). In brief, genotoxicity is now considered positive if the compound induces chromosomal aberrations at concentrations high enough to cause significant cytotoxicity (50% reduction in proliferation). Previously, signals from concentrations that caused cytotoxicity were not considered in the decision regarding genotoxicity. Using this revised criteria, both candesartan and its O-deethyl metabolite when evaluated using the Chinese hamster lung chromosomal aberration assay when evaluated in study 1582/GE, which was completed in 1994. This finding should be reflected in labeling (Dr. Proakis proposes language). Of note, candesartan and its metabolite were negative for genotoxicity in two *in vitro* mutagenesis assays as well as *in vitro* and *in vivo* chromosomal aberration tests (see Dr. Proakis' review, page 6).

#### SUMMARY

Dr. Proakis' recommendations should be transmitted to the sponsor in the form of recommended changes to labeling.

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this page is the manifestation of the electronic signature.**  
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/s/

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Doug Throckmorton  
7/24/02 02:34:46 PM  
MEDICAL OFFICER



**MEMORANDUM**

**DEPARTMENT OF HEALTH & HUMAN SERVICES  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research**

**DATE:** July 10, 2002

**FROM:** Abraham Karkowsky, M.D., Ph.D. Group Leader Division of Cardio-Renal Drug, Products HFD-110

**To:** Dr. Douglas Throckmorton, Director, Division of Cardio-Renal Drug Products, HFD-110

**SUBJECT:** Financial Disclosure by Clinical Investigators for Candasaratan NDA 20-838, Supplement #15 (submitted 27 September 2001).

AstraZeneca Pharmaceuticals LP submitted forms # 3454 for the investigators of the two pivotal studies #230 and #231. The sponsor asserts that it did not enter into any financial arrangements with the listed clinical investigators (attached list), whereby the value of compensation to the investigator could be affected by the outcome of the study. The sponsor also asserts that the investigators, who are required to disclose any proprietary interest in this product or a significant equity in the sponsor, did not disclose any such interests. The sponsor also certified that no listed investigator was the recipient of significant payments of other sorts.

Study # 175 is a supportive study for this application, which was completed before 2 February 1999. As such a modified form #3454 was submitted which deleted the criteria that the investigator received payments of other sorts.

Based on the absence of any financial interest of the involved investigators, the results of these three studies can be accepted.

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this page is the manifestation of the electronic signature.**  
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/s/

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Abraham Karkowsky  
7/9/02 03:32:14 PM  
MEDICAL OFFICER

## ITEM 19 FINANCIAL DISCLOSURE BY CLINICAL INVESTIGATORS

### Introduction

In accordance with 21 CFR Part 54, this section provides financial information for the adequate and well-controlled studies 175, 230, and 231. No other studies in this NDA are considered by the sponsor to be covered as defined by 21 CFR § 54.2(e). The clinical studies included in this financial disclosure are described in Table 1. Financial information reported in this item includes information provided to AstraZeneca (formerly Astra pharmaceuticals, LP) through 1 June 2001.

Study 175 was completed prior to 2 February 1999. The certification for this study is subject to the revisions in the requirements for financial disclosure set forth by FDA in the Federal Register, Rules and Regulations, 31 December 1998 (Volume 63, Number 251), pages 72171 - 72181. Consequently, information was collected regarding financial interests described in 21 CFR § 54.4(a)(3)(i) compensation affected by the outcome of clinical studies, 54.4(a)(3)(iii) proprietary interest in the tested product, and 54.4(a)(3)(iv) significant equity interest in Astra Pharmaceuticals LP, Astra AB, or Merck and Co., Inc. Through due diligence, it was determined that there were no disclosable financial interests. Therefore, Form FDA 3454 is being provided along with the list of investigators for this study in Table 2. It should be noted that Form FDA 3454 as published does not reflect the changes implemented in the 31 December 1998 revision. Therefore, Form FDA 3454 has been modified for Study 175 to line out the reference to significant payments of other sorts.

Studies 230 and 231 were completed after 2 February 1999. For these studies financial information was collected regarding the financial interests described in 21 CFR § 54.4(a)(3)(i) compensation affected by the outcome of clinical studies, 54.4(a)(3)(ii) significant payments of other sorts, 54.4(a)(3)(iii) proprietary interest in the tested product, and 54.4(a)(3)(iv) significant equity interest in Astra Pharmaceuticals LP, Astra AB or Merck & Co., Inc. Through due diligence, it was determined that there were no disclosable financial interests for outcome-based compensation, significant payments, or proprietary interests for studies 230 and 231. There were no investigators that reported significant equity interests. Therefore, Form FDA 3454 is being provided along with the list of investigators for these studies in Table 3.

Per 21 CFR §54.4(a)(3)(v), the steps taken by the study sponsor to minimize any potential bias for these studies include the following:

- Randomized – investigators could not influence which treatment a given patient would receive
- Double-blind - investigators and patients could not bias the results in favor of any given treatment, as all treatment assignments were blinded
- Multicenter - included 75 sites for Study 230, 75 sites for Study 231, and 45 sites for 175.

**TABLE 1**  
**Clinical Studies Included in Financial Disclosure**

Study No.	Sponsor	Location
230	AstraZeneca LP (formerly Astra Pharmaceuticals LP)	725 Chesterbrook Blvd. Wayne, PA 19087
231	AstraZeneca LP (formerly Astra Pharmaceuticals LP)	725 Chesterbrook Blvd. Wayne, PA 19087
175	AstraZeneca LP (formerly Astra Merck, Inc.)	725 Chesterbrook Blvd. Wayne, PA 19087

### CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. ~~I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).~~

Clinical Investigators	see attached list for Study 175	

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).
- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME Cindy M. Lancaster	TITLE Director, Regulatory Affairs
FIRM/ORGANIZATION AstraZeneca LP	
SIGNATURE <i>Cindy M. Lancaster</i>	DATE SEP 27 2001

#### Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services  
Food and Drug Administration  
5600 Fishers Lane, Room 14C-03  
Rockville, MD 20857

**TABLE 2**  
**Attachment to Form FDA 3454 for Study 175**  
**Certification: Financial Interests and Arrangements of Clinical Investigators**

Investigator	Mailing Address	P = Principal S = Subinvestigator	Study	Site
Allison, J. Richard	Carolina Research Associates 1333 Taylor Street, Suite 3B Columbia, SC 29201	P	175	039
Arnold, Stephen	Staub Clinic and Hospital 888 South King Street Honolulu, HI 996813	P	175	001
Aurigemma, Gerard P.	University of Massachusetts Medical Center Cardiology Division 55 Lake Avenue North Worcester, MA 01655	P	175	001
Bansal, Vinod K.	Loyola University Medical Center Division of Renal Disease and Hypertension 216 South First Avenue Maywood, IL 60153	P	175	002
Berk, Martin	Cardiovascular Research Institute of Dallas 7150 Greenville Avenue, Suite 650 Dallas, TX 75231	P	175	003
Bowling, Bruce T.	Endwell Family Physicians 415 Hooper Road Endwell, NY 13760	P	175	004
Bravo, Emmanuel	Cleveland Clinic Foundation Dept. of HTN, Neph. A101 9500 Euclid Avenue Cleveland, OH 44195	P	175	006
Bresnan, Paul	Watson Clinic, 2 East P.O. Box 95000 1600 Lakeland Hills Boulevard Lakeland, FL 33805	P	175	007
Chatman, Martin S.	Desert Foothills Medical Center 34115 North Scottsdale Road Scottsdale, AZ 85262	P	175	009
Damico, Peter	Lanier Education and Research Network 5925 Lovell Avenue Fort Worth, TX 76107	P	175	026
Deedwania, Prakash C.	Cardiology Division 111C 2615 East Clinton Avenue Fresno, CA 93703	P	175	010
Dreifus, Leonard	Central Florida Cardiology Group 500 East Colonial Drive Orlando, FL 32803	P	175	011

**TABLE 2 (Cont.)**  
**Attachment to Form FDA 3454 for Study 175**  
**Certification: Financial Interests and Arrangements of Clinical Investigators**

Investigator	Mailing Address	P = Principal S = Subinvestigator	Study	Site
Drucker, Jerry	Tampa Bay Medical Research Inc. 3253 McMullen Booth Rd. Suite 200 Clearwater, FL 34621	P	175	005
Dworkin, Lance D.	Rhode Island Hospital Aldrich 306 593 Eddy Street Providence, RI 02930	P	175	012
Ferguson, James	Pharmacology Research Corporation Commerce Park 448 East 6400 Street, Suite 350 Salt Lake City, UT 84107	P	175	016
Fisher, C.L.	TPMG Clinical Research Department 813 Diligence Drive, Suite 109 Newport News, VA 23606	P	175	017
Franklin, Jay	Texas Cardiology Consultants 712 North Washington, Suite 300 Dallas, TX 75246-1633	P	175	018
Fried, David L.	Omega Medical Research 400 Reservoir Avenue Providence, RI 02907	P	175	019
Fulcher, William	University Consortium for Clinical Research 516 Medical Towers Building 1717 11 <sup>th</sup> Avenue South Birmingham, AL 35294-4410	P	175	020
Gilderman, Larry	University Clinical Research Inc. 1150 North University Drive Pembroke, FL 33024	P	175	021
Gradman, Alan H.	The Western Pennsylvania Hospita 4800 Friendship Avenue, Suite 3411, North Tower Pittsburgh, PA 15224	P	175	022
Harris, Freeman	Oakridge Medical Clinic 4309 Oakridge Road Lake Oswego, OR 97035	P	175	023
Harris, Stuart I.	SeaView Research 951 LeJeune Road, Suite 304 Miami, FL 331334	P	175	035
Holmes, John A.	Heart of America Research Institute 5799 Broadmoor, Suite 138 Mission, KS 66202	P	175	008
Klein, Terry	Heartland Research Associates 1709 South Rock Road Wichita, KS 67207	P	175	025

**TABLE 2 (Cont.)**  
**Attachment to Form FDA 3454 for Study 175**  
**Certification: Financial Interests and Arrangements of Clinical Investigators**

Investigator	Mailing Address	P = Principal S = Subinvestigator	Study	Site
Levine, Barton	Nephrology Section (111L) VA Medical Center West L.A. 11301 Wilshire Boulevard Los Angeles, CA 90073	P	175	027
Lewin, Andrew	National Research Institute 2010 Wilshire Boulevard, Suite 404 Los Angeles, CA 90057	P	175	028
Lewis, James	Camino Medical Group, Sunnyvale Clinic 301 Old San Francisco Road Sunnyvale, CA 94086-6368	P	175	029
Littner, Michael	Sepulveda VAMC 111P-16111 Plummer Street Sepulveda, CA 91343	P	175	030
Loh, Irving	Ventura Heart Institute Research Office 215 West Janss Road Thousand, CA 91360	P	175	031
Montoro, Rafael	Clinical Therapeutics Corporation 470 Biltmore Way, Suite 102 Coral Gables, FL 33134	P	175	032
Mullican, William S.	MediSphere Medical Research Center LLC 1461 Professional Boulevard Evansville, IN 47714	P	175	033
Nocero, Michael	Central Florida Cardiology Group 500 East Colonial Drive Orlando, FL 32803	P	175	011
Oesterle, Robert	301 Health Park Boulevard, Suite 329 St. Augustine, FL 32086	P	175	014
Pappas, John E.	Central Kentucky Research Associates 2366 Nicholasville Road, Suite 602 Lexington, KY 40503	P	175	034
Patron, Andres	South Florida Clinical Research Center 6448 Pembroke Road Hollywood, FL 33023	P	175	036
Pratt, John H.	Hypertension Research Center Long Clinical- Room 429 541 Clinical Drive Indianapolis, IN 46202-5111	P	175	037
Punzi, Henry	Trinity Hypertension Research Center 4333 North Josey Lane, Suite 300 Carrollton, TX 75010	P	175	038

**TABLE 2 (Cont.)**  
**Attachment to Form FDA 3454 for Study 175**  
**Certification: Financial Interests and Arrangements of Clinical Investigators**

Investigator	Mailing Address	P = Principal S = Subinvestigator	Study	Site
Rosen, Jeff	Clinical Research of South Florida 299 Alhambra Circle Coral Gables, FL 33134	P	175	040
Shearer, Cameron	Clinical Research Associates, Inc. 2222 State Street, Suite D Nashville, TN 37203	P	175	041
Sievers II, Richard J.	Dayton Area Research Associates 505A East Stroop Road Kettering, OH 45429	P	175	015
Smith, William B.	New Orleans Center for Clinical Research 2820 Canal Street New Orleans, LA 70119	P	175	042
Tonkon, Melvin	Anaheim Heart and Research Institute 1211 West La Palma, Suite 207 Anaheim, CA 92801	P	175	043
Vogelbach, Heiner	Huntington Memorial Hospital Department of Cardiology 100 West California Boulevard Pasadena, CA 91105	P	175	044
Weinberg, Marc	Gambro Healthcare, Hypertension and Nephrology 125 Corliss Street Providence, RI 02904	P	175	024
Yellen, Lawrence	Cardiology Associates Medical Group 5555 Reservoir Drive, Suite 209 San Diego, CA 92120	P	175	045

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Clinical Investigators	see attached list for Studies 230 & 231	

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).
- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME Cindy M. Lancaster	TITLE Director, Regulatory Affairs
FIRM/ORGANIZATION AstraZeneca LP	
SIGNATURE 	DATE SEP 27 2001

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Department of Health and Human Services  
Food and Drug Administration  
5600 Fishers Lane, Room 14C-03  
Rockville, MD 20857

**TABLE 3**  
**Attachment to Form FDA 3454 for Studies 230 and 231**  
**Certification: Financial Interests and Arrangements of Clinical Investigators**

Investigator	Mailing Address	P = Principal S = Subinvestigator	Study	Site
		S	230	019
		S	230	045
		S	230	059
		S	230	057
		S	230	014
		S	230	062
		S	230	004
		S	230	071
		S	230	059
		S	230	016
		S	230	014
Baratta, Frank G.	1880 East Commercial Boulevard Fort Lauderdale, FL 33308	P	230	062

**TABLE 3 (Cont.)**  
**Attachment to Form FDA 3454 for Studies 230 and 231**  
**Certification: Financial Interests and Arrangements of Clinical Investigators**

Investigator	Mailing Address	P = Principal S = Subinvestigator	Study	Site
		S	230	055
		S	230	063
		S	230	073
		S	230	019
		S	230	060
		S	230	034
		S	230	070
Bleser, Scott	Midwest Regional Research, Inc. 4336 State Route 725 Bellbrook, OH 45305-1551	P	230	001
		S	230	081
		S	230	060
		S	230	003
		S	230	082

**TABLE 3 (Cont.)**  
**Attachment to Form FDA 3454 for Studies 230 and 231**  
**Certification: Financial Interests and Arrangements of Clinical Investigators**

Investigator	Mailing Address	P = Principal S = Subinvestigator	Study	Site
		S	230	063
Bresnan, Paul	Watson Clinic, 2 East P.O. Box 95000 1600 Lakeland Hills Boulevard Lakeland, FL 33805	P	230	063
Brigham, Joan	ICSL-Clinical Studies 201 Providence Road, Suite 102 Charlotte, NC 28207	P	230	007
		S	230	044
		S	230	026
		S	230	047
		S	230	059
		S	230	063
		S	230	065
		S	230	063
		S	230	065
Calhoun, David	University of Alabama at Birmingham 933 South 19 <sup>th</sup> Street, Room 115 Birmingham, AL 35294-2041	P	230	014
		S	230	060

**TABLE 3 (Cont.)**  
**Attachment to Form FDA 3454 for Studies 230 and 231**  
**Certification: Financial Interests and Arrangements of Clinical Investigators**

Investigator	Mailing Address	P = Principal S = Subinvestigator	Study	Site
		S	230	019
		S	230	044
		S	230	067
		S	230	066
		S	230	038
		S	230	044
		S	230	062
		S	230	020
		S	230	001
		S	230	063
Conway, Martin	Lovelace Scientific Research 2441 Ridgecrest Drive, S.E. Albuquerque, NM 87108	P	230	082
		S	230	025

**TABLE 3 (Cont.)**  
**Attachment to Form FDA 3454 for Studies 230 and 231**  
**Certification: Financial Interests and Arrangements of Clinical Investigators**

Investigator	Mailing Address	P = Principal S = Subinvestigator	Study	Site
		S	230	073
Craven, Pamela	Health Advance Institute 1004 SW 44 <sup>th</sup> Street, 2 <sup>nd</sup> Floor Oklahoma City, OK 73109	P	230	057
Cushman, William	VAMC-Memphis, Room CW513 1030 Jefferson Avenue Memphis, TN 38104	P	230	032
		S	230	045
		S	230	044
D'Amico, Stephen	GRAE, Inc. 2001 Mallory Lane, Suite 203 Franklin, TN 37607	P	230	041
		S	230	079
		S	230	054
		S	230	048
		S	230	012
		S	230	060
DeQuattro, Vincent	2250 Alcazar Street, CSC-116 Los Angeles, CA 90089-9065	P	230	008
		S	230	072

**TABLE 3 (Cont.)**  
**Attachment to Form FDA 3454 for Studies 230 and 231**  
**Certification: Financial Interests and Arrangements of Clinical Investigators**

Investigator	Mailing Address	P = Principal S = Subinvestigator	Study	Site
		S	230	028
Downey, Julie	Jefferson County Medical Clinic, PA 302 Madison Street Oskaloosa, KS 66066-0305	P	230	069
		S	230	026
		S	230	060
Dworkin, Lance D.	Rhode Island Hospital Aldrich 306 593 Eddy Street Providence, RI-02903	P	230	042
		S	230	063
		S	230	072
		S	230	025
		S	230	060
		S	230	018
		S	230	026
		S	230	047

**TABLE 3 (Cont.)**  
**Attachment to Form FDA 3454 for Studies 230 and 231**  
**Certification: Financial Interests and Arrangements of Clinical Investigators**

Investigator	Mailing Address	P = Principal S = Subinvestigator	Study	Site
		S	230	055
		S	230	045
		S	230	057
		S	230	062
		S	230	065
Frid. David J.	OSU Center for Wellness and Prevention 2050 Kenny Road, Suite 1010 Columbus, OH 43221-3500	P	230	017
Friesen, Debra Ann	Exempla Internal Medicine 2550 Lutheran Parkway, Suite G-20 Wheat Ridge, CO 80033	P	230	079
Garland, W. Thomas	Lawrence Clinical Research 3100 Princeton Pike Building 1, 3 <sup>rd</sup> Floor, Suite J Lawrenceville, NJ 08648	P	230	002
		S	230	021
		S	230	032
		S	230	032
		S	230	033

**TABLE 3 (Cont.)**  
**Attachment to Form FDA 3454 for Studies 230 and 231**  
**Certification: Financial Interests and Arrangements of Clinical Investigators**

Investigator	Mailing Address	P = Principal S = Subinvestigator	Study	Site
Gilderman, Larry	University Clinical Research Inc. 1150 North University Drive Pembroke, FL 33024	P	230	010
Gillie, Edward	Medical Studies, Florida 12751 New Brittany Boulevard. Suite 501 Fort Meyers, FL 33907	P	230	033
		S	230	063
Goldsmith, Ivan	West Trop Medical Centre 4845 South Rainbow Boulevard. Suite 401 Las Vegas, NV 89103	P	230	077
		S	230	
		S	230	063
		S	230	003
Gove, Richard C.	Jersey Research Foundation, Inc. 222 New Road, #302 Linwood, NJ 08221	P	230	066
		S	230	054
Gutierrez, Maria	ICSL-Clinical Studies 500 SE 17 <sup>th</sup> Street, Suite 100 Fort Lauderdale, FL 33316	P	230	018
		S	230	062
		S	230	057
		S	230	065

**TABLE 3 (Cont.)**  
**Attachment to Form FDA 3454 for Studies 230 and 231**  
**Certification: Financial Interests and Arrangements of Clinical Investigators**

Investigator	Mailing Address	P = Principal S = Subinvestigator	Study	Site
Harvey, Kathy	Internal Medicine 140 Stollings Avenue, Suite 2 Logan, WV 25601	P	230	064
Heppner, Bradley	ICSL-Clinical Studies 5750 Centre Avenue, Suite 230 Pittsburgh, PA 15206	P	230	034
Holmes, John A.	Heart of America Research Institute 5799 Broadmoor Ste. 138 Mission, KS 66202	P	230	053
		S	230	060
		S	230	017
Hood, Walter E.	ICSL-Clinical Studies 6065 Roswell Road, Suite 820 Atlanta, GA 30328	P	230	003
		S	230	060
Jack, David B.	Physicians Research Options 10011 South Centennial Parkway, Suite 360 Sandy, UT 84070	P	230	004
		S	230	060
		S	230	060
Jacobson, Edwin	100 UCLA Medical Plaza, #690 Los Angeles, CA 90095	P	230	011
Jain, Ashok	18181 Oakwood Boulevard, Suite 303 Dearborn, MI 48124	P	230	050
		S	230	067

**TABLE 3 (Cont.)**  
**Attachment to Form FDA 3454 for Studies 230 and 231**  
**Certification: Financial Interests and Arrangements of Clinical Investigators**

Investigator	Mailing Address	P = Principal S = Subinvestigator	Study	Site
		S	230	063
		S	230	024
		S	230	048
		S	230	051
Kaplan, Roy	East Bay Clinical Trial 2700 Grant Street, #200 Concord, CA 94520	P	230	054
		S	230	063
		S	230	028
		S	230	036
Kerwin, Edward M.	Clinical Research Institute of Southern Oregon, LLC 832 East Main, Suite 7 Medford, OR 97504	P	230	012
		S	230	
		S	230	054
		S	230	073
		S	230	055

**TABLE 3 (Cont.)**  
**Attachment to Form FDA 3454 for Studies 230 and 231**  
**Certification: Financial Interests and Arrangements of Clinical Investigators**

Investigator	Mailing Address	P = Principal S = Subinvestigator	Study	Site
Kloner, Robert	Los Angeles Cardiology Associates 1245 Wilshire Boulevard, Suite 703 Los Angeles, CA 90017	P	230	019
		S	230	077
		S	230	053
		S	230	060
		S	230	048
		S	230	059
		S	230	041
Leff, Robert	Hill Top Argus Research, Inc. 7042 East Broadway Tucson, AZ 85710	P	230	059
Lefton, Theodore E.	ICSL-Clinical Studies 1360 Sarno Road, Suite B Melbourne, FL 32935	P	230	049
		S	230	003
		S	230	019
Levin, Alan	395 Saratoga Road Glenville, NY 12302	P	230	078
		S	230	008

**TABLE 3 (Cont.)**  
**Attachment to Form FDA 3454 for Studies 230 and 231**  
**Certification: Financial Interests and Arrangements of Clinical Investigators**

Investigator	Mailing Address	P = Principal S = Subinvestigator	Study	Site
		S	230	059
		S	230	006
		S	230	022
		S	230	028
		S	230	044
		S	230	025
		S	230	019
Malik, Hari	Cedarwood Medical Center 820 Lester Avenue St. Joseph, MI 49085	P	230	006
		S	230	071
		S	230	024
		S	230	062
Marcadis, Abe	ICSL-Clinical Studies 8200 Jog Road, Suite 101 Boyton Beach, FL 34652	P	230	020
		S	230	066

**TABLE 3 (Cont.)**  
**Attachment to Form FDA 3454 for Studies 230 and 231**  
**Certification: Financial Interests and Arrangements of Clinical Investigators**

Investigator	Mailing Address	P = Principal S = Subinvestigator	Study	Site
		S	230	019
		S	230	067
		S	230	019
McAllister, R. Eric	MEDStudies, Inc. 691 South Dora Street Ukiah, CA 95482-5426	P	230	005
		S	230	029
		S	230	069
		S	230	055
		S	230	034
Mihalik, John	Northern California Medical Associates 6 Tarman Drive Cloverdale, CA 95425	P	230	016
		S	230	045
Miller, David	Bucks County Clinical Research 201 Woolston Drive Morrisville, PA 19067	P	230	047
		S	230	034

**TABLE 3 (Cont.)**  
**Attachment to Form FDA 3454 for Studies 230 and 231**  
**Certification: Financial Interests and Arrangements of Clinical Investigators**

Investigator	Mailing Address	P = Principal S = Subinvestigator	Study	Site
Miller, Michael	University of Maryland School of Medicine Division of Cardiology 22 South Greene Street, S3B06 Baltimore, MD 21201	P	230	080
		S	230	010
		S	230	080
Montoro, Rafael	Clinical Therapeutics Corporation 470 Baltimore Way, Suite 102 Coral Gables, FL 33134	P	230	022
		S	230	015
Mossberg, Jane	Research Studies 1180 Patterson Street, Suite 3B Eugene, OR 97401	P	230	043
Mroczek, William	Clinical Research of Northern Virginia 6051A Arlington Boulevard Falls Church, VA 22044	P	230	055
Mulholland, David	Hill Top Med Quest Research 552A Memorial Drive Ext Greer, SC 29651	P	230	065
		S	230	062
		S	230	080
		S	230	062
		S	230	056

**TABLE 3 (Cont.)**  
**Attachment to Form FDA 3454 for Studies 230 and 231**  
**Certification: Financial Interests and Arrangements of Clinical Investigators**

Investigator	Mailing Address	P = Principal S = Subinvestigator	Study	Site
		S	230	063
Neuman, Larry	4120 Broadway New York, NY 10033	P	230	070
		S	230	057
		S	230	081
		S	230	045
Nunez, Margarita C.	ICSL-Clinical Studies 780 94 <sup>th</sup> Avenue North, Suite 102 St. Petersburg, FL 33702	P	230	035
O'Barr, Thomas	Health Advance Institute 1431 White Circle Marietta, GA 30066	P	230	044
		S	230	082
		S	230	003
		S	230	055
Okusa, Mark	University of Virginia Hospital 5 <sup>th</sup> Floor McIntyre Wing, Hospital West, Room 5504C Charlottesville, VA 22908	P	230	081
		S	230	018
		S	230	014

**TABLE 3 (Cont.)**  
**Attachment to Form FDA 3454 for Studies 230 and 231**  
**Certification: Financial Interests and Arrangements of Clinical Investigators**

Investigator	Mailing Address	P = Principal S = Subinvestigator	Study	Site
		S	230	077
Papademetriou, Vasilios	VAMC-Hypertension Research Clinic 151 E 50 Irving Street NW Washington, D.C. 20422	P	230	056
		S	230	081
		S	230	032
		S	230	019
		S	230	041
		S	230	026
Persaud, Kavita	St. Joseph Senior Health Services 800 Broadway, Suite 115 Fort Wayne, IN 46802	P	230	051
Pettyjohn, Frank	University of South Alabama 3401 Medical Park Drive Building 3, Suite 107 Mobile, AL 36693	P	230	073
		S	230	028
		S	230	019
Pool, James L.	Baylor College of Medicine- Methodist Hospital 6565 Fannin MS F504, Suite 531 Houston, TX 77030	P	230	052

**TABLE 3 (Cont.)**  
**Attachment to Form FDA 3454 for Studies 230 and 231**  
**Certification: Financial Interests and Arrangements of Clinical Investigators**

Investigator	Mailing Address	P = Principal S = Subinvestigator	Study	Site
		S	230	004
		S	230	004
		S	230	057
Puopolo, Anthony	Milford Emergency Associates. Inc. 5 Water Street Milford, MA 01757	P	230	023
		S	230	063
Rahman, Mahboob	University Hospitals of Cleveland 11100 Euclid Avenue Cleveland, OH 44106-6053	P	230	072
		S	230	035
		S	230	010
		S	230	025
		S	230	081
Raval, Pramod	24661 Coolidge Highway Oak Park, MI 48237	P	230	024
		S	230	068

**TABLE 3 (Cont.)**  
**Attachment to Form FDA 3454 for Studies 230 and 231**  
**Certification: Financial Interests and Arrangements of Clinical Investigators**

Investigator	Mailing Address	P = Principal S = Subinvestigator	Study	Site
Razzetti, Albert J.	University Clinical Research- DeLand 925 North Spring Garden Avenue DeLand, FL 32720-2560	P	230	025
		S	230	063
		S	230	029
Ripley, Elizabeth	Medical College Campus of VA Commonwealth University 1101 East Marshall Street Sangar Hall, Room 8-062 Richmond, VA 23298	P	230	021
		S	230	077
		S	230	004
		S	230	059
Rosansky, Steven	Three Rivers Medical-Carolina Research Assoc. 1301 Taylor Street, Suite 2H Columbia, SC 29201	P	230	058
Rose, Herman	1315 Sixth Avenue Fort Worth, TX 76104	P	230	076
Roth, Eli	Sterling Research Group, Ltd. 2230 Auburn Avenue, Level B Cincinnati, OH 45219	P	230	036
Rothschild, Henry	Louisiana State Medical Center 1542 Tulane Avenue, A317 New Orleans, LA 70112	P	230	037
Rubino, John	Raleigh Medical Group 3521 Haworth Drive Raleigh, NC 27609	P	230	060

**TABLE 3 (Cont.)**  
**Attachment to Form FDA 3454 for Studies 230 and 231**  
**Certification: Financial Interests and Arrangements of Clinical Investigators**

Investigator	Mailing Address	P = Principal S = Subinvestigator	Study	Site
		S	230	062
		S	230	032
		S	230	022
Savage, Susan	ICSL-Clinical Studies 1873 South Bellaire Street, Suite 1100 Denver, CO 80222	P	230	026
		S	230	045
		S	230	033
		S	230	059
		S	230	025
Scully, Kevin T.	Lexington Cardiology Consultants 1760 Nicholasville Road, Suite 601 Lexington, KY 40503	P	230	038
		S	230	045
		S	230	042
		S	230	019

**TABLE 3 (Cont.)**  
**Attachment to Form FDA 3454 for Studies 230 and 231**  
**Certification: Financial Interests and Arrangements of Clinical Investigators**

Investigator	Mailing Address	P = Principal S = Subinvestigator	Study	Site
		S	230	021
		S	230	063
Slabic, Stan	Slabic and Slabic Internal Medicine 1334 West 38 <sup>th</sup> Street Erie, PA 16508	P	230	039
Smith, William B.	New Orleans Center for Clinical Research 2820 Canal Street New Orleans, LA 70119	P	230	067
		S	230	004
		S	230	053
		S	230	079
		S	230	004
		S	230	073
Stoukides, John A.	ICSL-Clinical Studies 40 Hemingway Drive East Providence, RI 02915	P	230	045
		S	230	020

**TABLE 3 (Cont.)**  
**Attachment to Form FDA 3454 for Studies 230 and 231**  
**Certification: Financial Interests and Arrangements of Clinical Investigators**

Investigator	Mailing Address	P = Principal S = Subinvestigator	Study	Site
		S	230	079
		S	230	004
		S	230	052
		S	230	059
		S	230	052
Taylor, Malcolm	Jackson Cardiology Associates, P.A. 971 Lakeland Drive, Suite 850 Jackson, MS 39216	P	230	068
		S	230	032
		S	230	045
Tse, Thomas	311 West Lincoln, Suite 201 Bellville, IL 62220	P	230	046
		S	230	055
		S	230	057
		S	230	048

**TABLE 3 (Cont.)**  
**Attachment to Form FDA 3454 for Studies 230 and 231**  
**Certification: Financial Interests and Arrangements of Clinical Investigators**

Investigator	Mailing Address	P = Principal S = Subinvestigator	Study	Site
		S	230	060
		S	230	016
Vidt, Donald	Cleveland Clinic Foundation Department of HTN/Nephrology A101 9500 Euclid Avenue Cleveland, OH 44195	P	230	075
		S	230	063
Wagner, Margaret	2001 South Woodruff, Suite 15 Idaho Falls, ID 83404	P	230	027
		S	230	054
		S	230	008
		S	230	
Weerasinghe, Mervyn	Rochester Clinical Research 500 Helendale Road, Suite L20 Rochester, NY 14609	P	230	048
Wehle, Susan	ICSL-Clinical Studies 1387 Oak Field Drive Brandon, FL 33511	P	230	028
White, William	University of Connecticut Health Center 263 Farmington Avenue Farmington, CT 06030-3940	P	230	071
		S	230	055
Wolfley, Gerald D.	Hill Top Research, Inc. 7555 East Osborn Road, Suite 200 Scottsdale, AZ 85251	P	230	029

**TABLE 3 (Cont.)**  
**Attachment to Form FDA 3454 for Studies 230 and 231**  
**Certification: Financial Interests and Arrangements of Clinical Investigators**

Investigator	Mailing Address	P = Principal S = Subinvestigator	Study	Site
		S	230	072
		S	230	077
		S	230	063
		S	230	067
		S	230	067

**TABLE 3 (Cont.)**  
**Attachment to Form FDA 3454 for Studies 230 and 231**  
**Certification: Financial Interests and Arrangements of Clinical Investigators**

Investigator	Mailing Address	P = Principal S = Subinvestigator	Study	Site
Abdelghany, Amin	City Medical Center 340 West 23 <sup>rd</sup> Street, Suite B Panama City, FL 32405	P	231	260
		S	231	267
		S	231	269
Adolphe, Allen B.	Internal Medicine 2901 Georgia NE, Suite C4 Albuquerque, NM 87110	P	231	261
		S	231	228
Allison, J. Richard	Carolina Research Associates 1333 Taylor Street, Suite 3B Columbia, SC 29201	P	231	221
A		S	231	212
		S	231	256
		S	231	253
		S	231	220
		S	231	229
Bakris, George	Rush-Presbyterian St. Luke's Medical Center Clinical Research Center 1700 West Van Buren Chicago, IL 60612	P	231	263

**TABLE 3 (Cont.)**  
**Attachment to Form FDA 3454 for Studies 230 and 231**  
**Certification: Financial Interests and Arrangements of Clinical Investigators**

Investigator	Mailing Address	P = Principal S = Subinvestigator	Study	Site
		S	231	271
		S	231	253
Bear, Norse	Cornerstone Clinical Research, Inc. 2225 Downingly Street Denver, CO 80205	P	231	253
Beathe, Janet	1480 West Center Essexville, MI 48732	P	231	265
		S	231	233
		S	231	269
Buchanan, Patricia	River Road Medical Group 890 River Road Eugene, OR 97404	P	231	224
Burleson, Michael	3115 G Street Eureka, CA 95503	P	231	257
Carr, Larry L.	1610 South Euclid Avenue Bay City, MI 48706	P	231	249
		S	231	254
Cattan, Rogelio	Lifespan Research Foundation, Inc. 8750 SW 144 Street, Suite 203 Miam, FL 33176	P	231	232
		S	231	250
Chandler, Bronell	6800 Market Street Upper Darby, PA 19082	P	231	242

**TABLE 3 (Cont.)**  
**Attachment to Form FDA 3454 for Studies 230 and 231**  
**Certification: Financial Interests and Arrangements of Clinical Investigators**

Investigator	Mailing Address	P = Principal S = Subinvestigator	Study	Site
		S	231	250
		S	231	218
		S	231	202
Christensen, Shane	Clinical Research Advantage, Inc. Foothill Family Clinic South 6360 South 3000 East Salt Lake City, UT 84121	P	231	268
		S	231	210
Chrysant, Steven G.	Oklahoma Cardiovascular and Hypertension Center 5850 West Wilshire Boulevard Oklahoma City, OK 73132-4904	P	231	210
		S	231	253
		S	231	243
		S	231	271
		S	231	268
Conrad, James L.	TriValley Primary Care: Pennridge Office 1301 North 5 <sup>th</sup> Street Perkasie, PA 18994	P	231	082
		S	231	226

**TABLE 3 (Cont.)**  
**Attachment to Form FDA 3454 for Studies 230 and 231**  
**Certification: Financial Interests and Arrangements of Clinical Investigators**

Investigator	Mailing Address	P = Principal S = Subinvestigator	Study	Site
		S	231	253
Com. Lydia	ICSL-Clinical Studies 5969 Cattleridge Boulevard. Suite 100 Sarasota. FL 34232	P	231	243
		S	231	214
Cronin. Pamela	VANTHCS (11) 4500 South Lancaster Road Dallas. TX 75216	P	231	266
		S	231	245
Curland. Steven	118 New London Turnpike Norwich. CT 06360	P	231	241
Dachman. William	Vista Medical Research, Inc. 3940 East University, Suite 4 Mesa. AZ 85205	P	231	233
D'Adezzio. Carmella	1480 West Center Essexville. MI 48732	P	231	265
Dadourian. Berge	Nevada Cardiology Associates 3121 South Maryland Parkway. Suite 512 Las Vegas. NV 89109	P	231	236
		S	231	262
		S	231	256
		S	231	215

**TABLE 3 (Cont.)**  
**Attachment to Form FDA 3454 for Studies 230 and 231**  
**Certification: Financial Interests and Arrangements of Clinical Investigators**

Investigator	Mailing Address	P = Principal S = Subinvestigator	Study	Site
		S	231	082
		S	231	082
		S	231	224
		S	231	216
Denny, D. Marty	River Cities Cardiology 207 Sparks Avenue, Suite 104 Jeffersonville, IN 47130	P	231	235
		S	231	231
		S	231	266
		S	231	274
		S	231	229
		S	231	275
Drehobl, Margaret	Scripps Clinic 15025 Innovation Drive San Diego, CA 92128	P	231	234
		S	231	267

**TABLE 3 (Cont.)**  
**Attachment to Form FDA 3454 for Studies 230 and 231**  
**Certification: Financial Interests and Arrangements of Clinical Investigators**

Investigator	Mailing Address	P = Principal S = Subinvestigator	Study	Site
		S	231	218
		S	231	240
		S	231	234
Ferrer, Bonafacio	West Park Medical Center 14307 Puritas Avenue, Unit D Cleveland, OH 44135	P	231	276
Fletcher, Anthony M.	Cardiology and Medicine Clinic, P.A. 5315 West 12 <sup>th</sup> Street Little Rock, AR 72204	P	231	259
		S	231	268
		S	231	245
		S	231	272
		S	231	272
Fried, David L.	Omega Medical Research 400 Reservoir Avenue Providence, RI 02907	P	231	238
		S	231	254

**TABLE 3 (Cont.)**  
**Attachment to Form FDA 3454 for Studies 230 and 231**  
**Certification: Financial Interests and Arrangements of Clinical Investigators**

Investigator	Mailing Address	P = Principal S = Subinvestigator	Study	Site
		S	231	240
		S	231	267
		S	231	226
		S	231	243
Gradman, Alan H.	The Western Pennsylvania Hospital 4800 Friendship Avenue, Suite 3411, North Tower Pittsburgh, PA 15224	P	231	267
Gravenstein, Stefan	The Glennan Center for Geriatrics and Gerontology Hofheimer Hall, Suite 202 825 Fairfax Avenue Norfolk, VA 23507-1912	P	231	272
		S	231	274
		S	231	228
		S	231	256
		S	231	228
		S	231	259

**TABLE 3 (Cont.)**  
**Attachment to Form FDA 3454 for Studies 230 and 231**  
**Certification: Financial Interests and Arrangements of Clinical Investigators**

Investigator	Mailing Address	P = Principal S = Subinvestigator	Study	Site
		S	231	269
		S	231	259
Hams, H. Freeman	Oakridge Medical Center 4309 Oakridge Road Lake Oswego, OR 97035	P	231	201
Harris, Stuart I.	SeaView Research 951 LeJeune Road, Suite 304 Miami, FL 33134	P	231	201
Hart, Terence	203 West Avalon Avenue, Suite 230 Muscle Shoals, AL 35662	P	231	255
		S	231	239
		S	231	267
		S	231	238
		S	231	267
		S	231	240
		S	231	215

**TABLE 3 (Cont.)**  
**Attachment to Form FDA 3454 for Studies 230 and 231**  
**Certification: Financial Interests and Arrangements of Clinical Investigators**

Investigator	Mailing Address	P = Principal S = Subinvestigator	Study	Site
		S	231	256
		S	231	267
		S	231	233
Horwitz, Lawrence	University of Colorado Health Science Center 4200 East Ninth Avenue Department of Cardiology, Box B- 130 Denver, CO 80262	P	231	237
		S	231	259
Jaffer, Nazim A.	Internal Medicine 4308 Belmont Avenue Youngstown, OH 44505	P	231	219
		S	231	267
		S	231	232
		S	231	256
		S	231	269

**TABLE 3 (Cont.)**  
**Attachment to Form FDA 3454 for Studies 230 and 231**  
**Certification: Financial Interests and Arrangements of Clinical Investigators**

Investigator	Mailing Address	P = Principal S = Subinvestigator	Study	Site
		S	231	217
		S	231	217
		S	231	218
		S	231	216
Katz, Lois Anne	Department of Veterans Affairs Medical Center (11A) New York Harbor Healthcare System; NY Campus 423 East 23 <sup>rd</sup> Street New York, NY 10010	P	231	225
		S	231	215
		S	231	250
		S	231	269
		S	231	256
Kipperman, Robert	Oklahoma Foundation for Cardiovascular Research 711 Stanton L. Young Boulevard. #100 Oklahoma City, OK 73104	P	231	239
		S	231	205

**TABLE 3 (Cont.)**  
**Attachment to Form FDA 3454 for Studies 230 and 231**  
**Certification: Financial Interests and Arrangements of Clinical Investigators**

Investigator	Mailing Address	P = Principal S = Subinvestigator	Study	Site
Klein, Thomas C.	Heartland Research Associates 7602 East Harry Wichita, KS 67207	P	231	205
		S	231	218
Kopyt, Nelson	Northeast Clinical Research Center 4825 Tilghman Street, Suite 101 Allentown, PA 18104	P	231	217
		S	231	267
Kovach, Julie A.	VA Medical Center Cardiology 111A 2215 Fuller Road Ann Arbor, MI 48105	P	231	271
		S	231	228
		S	231	228
Lafata, John	Northeast Count Internal Medicine 2067 West Vista, #200 & 200A Vista, CA 92083	P	231	256
		S	231	273
Lanier, Bobby Quentin	Lanier Education and Research Network 5925 Lovell Avenue Fort Worth, TX 76107	P	231	262
Lasseter, Kenneth	Clinical Pharmacology Associates 2060 NW 22 <sup>nd</sup> Avenue Miami, FL 33142	P	231	247
		S	231	254

**TABLE 3 (Cont.)**  
**Attachment to Form FDA 3454 for Studies 230 and 231**  
**Certification: Financial Interests and Arrangements of Clinical Investigators**

Investigator	Mailing Address	P = Principal S = Subinvestigator	Study	Site
		S	231	256
		S	231	273
		S	231	082
		S	231	256
		S	231	226
		S	231	256
Lewin, Andrew	National Research Institute 2010 Wilshire Boulevard, Suite 404 Los Angeles, CA 90057	P	231	207
		S	231	268
		S	231	243
		S	231	218
		S	231	268
		S	231	211

**TABLE 3 (Cont.)**  
**Attachment to Form FDA 3454 for Studies 230 and 231**  
**Certification: Financial Interests and Arrangements of Clinical Investigators**

Investigator	Mailing Address	P = Principal S = Subinvestigator	Study	Site
Maravel, Richard	5340 Gulf Drive, Suite 203 New Port Richey, FL 34652	P	231	212
		S	231	211
		S	231	206
		S	231	230
		S	231	272
		S	231	272
		S	231	239
		S	231	245
McKeever, Clark D.	Health Advance Institute 902 Frostwood, Suite 315 Houston, TX 77024	P	231	252
McKenna, Douglas	118 New London Turnpike Norwich, CT 06360	P	231	241
		S	231	253
		S	231	212

**TABLE 3 (Cont.)**  
**Attachment to Form FDA 3454 for Studies 230 and 231**  
**Certification: Financial Interests and Arrangements of Clinical Investigators**

Investigator	Mailing Address	P = Principal S = Subinvestigator	Study	Site
		S	231	208
		S	231	204
		S	231	250
Mirani, Mahendra	152 Lake Street Hamburg, NY 14075	P	231	213
		S	231	229
Mohan, K. K.	1480 West Center Essexville, MI 48732	P	231	265
		S	231	082
		S	231	256
		S	231	205
Morton, Jeffrey S.	5401 North Knoxville, #48 Peoria, IL 61614	P	231	258
		S	231	215
Mullican, William S.	MediSphere Medical Research Center LLC 1461 Professional Boulevard Evansville, IN 47714	P	231	240
		S	231	250

**TABLE 3 (Cont.)**  
**Attachment to Form FDA 3454 for Studies 230 and 231**  
**Certification: Financial Interests and Arrangements of Clinical Investigators**

Investigator	Mailing Address	P = Principal S = Subinvestigator	Study	Site
Myers, Edward	2581 North Road NE Warren, OH 44483	P	231	203
Narayan, Puneet	Clinical Research Institute of Northern Virginia 5514 Alma Lane, Suite 301 Springfield, VA 22151	P	231	211
		S	231	248
Nash, Stephen	Presidential Plaza, Suite 204 600 East Genesee Street Syracuse, NY 13202	P	231	248
		S	231	082
		S	231	216
Nayak, Nicholas	ICSL-Clinical Studies 1300 Franklin Avenue, Suite 180 Normal, IL 61761	P	231	216
		S	231	268
		S	231	202
		S	231	250
		S	231	261
		S	231	275

**TABLE 3 (Cont.)**  
**Attachment to Form FDA 3454 for Studies 230 and 231**  
**Certification: Financial Interests and Arrangements of Clinical Investigators**

Investigator	Mailing Address	P = Principal S = Subinvestigator	Study	Site
		S	231	267
		S	231	247
Ou, Kuang	7405 Irvine Street Pittsburgh, PA 15218	P	231	056
		S	231	215
		S	231	222
		S	231	211
Pappas, John E.	Central Kentucky Research Associates 2366 Nicholasville Road, Suite 602 Lexington, KY 40503	P	231	215
Passer, Jeffrey	9300 Underwood, Suite 520 Omaha, NE 68114	P	231	264
Patron, Andres	South Florida Clinical Research Center 6448 Pembroke Road Hollywood, FL 33023	P	231	209
		S	231	222
		S	231	252

**TABLE 3 (Cont.)**  
**Attachment to Form FDA 3454 for Studies 230 and 231**  
**Certification: Financial Interests and Arrangements of Clinical Investigators**

Investigator	Mailing Address	P = Principal S = Subinvestigator	Study	Site
		S	231	243
		S	231	082
Phillips, Robert A.	Mount Sinai Medical Center One Gustave L. Levy Place: Box 1085 New York, NY 10029-6574	P	231	274
Pinnas, Jacob	Arizona Clinical Studies 32 Medical Square 1601 North Tuscon Boulevard Tuscon, AZ 85716	P	231	214
		S	231	208
		S	231	205
		S	231	082
Rabetoy, Gary	University of Utah Department of Pharmacy Practice 20-S 2000 East #258 Salt Lake City, UT 84112-5820	P	231	250
		S	231	274
		S	231	272
Reif, Max	University of Cincinnati, Hypertension Section 231 Bathesda Avenue, K-Pavilion Room 401 Cincinnati, OH 45267-0565	P	231	254

**TABLE 3 (Cont.)**  
**Attachment to Form FDA 3454 for Studies 230 and 231**  
**Certification: Financial Interests and Arrangements of Clinical Investigators**

Investigator	Mailing Address	P = Principal S = Subinvestigator	Study	Site
		S	231	202
		S	231	228
Rhoades, Robert B.	Medical Parameters 4485 Columbia Road, Suite 300 Martinez, GA 30907	P	231	245
		S	231	230
Ripley, Peter M.	ICSL-Clinical Studies 23H White's Path South Yarmouth, MA 02664	P	231	230
		S	231	256
		S	231	261
Rosen, Jeffrey	Clinical Research of South Florida 299 Alhambra Circle Coral Gables, FL 33134	P	231	229
		S	231	237
		S	231	211
Ruff, Dennis	Healthcard Discoveries, PA 5282 Medical Drive, Suite 614 San Antonio, TX 78229	P	231	231
		S	231	212
		S	231	233

**TABLE 3 (Cont.)**  
**Attachment to Form FDA 3454 for Studies 230 and 231**  
**Certification: Financial Interests and Arrangements of Clinical Investigators**

Investigator	Mailing Address	P = Principal S = Subinvestigator	Study	Site
		S	231	275
		S	231	247
		S	231	240
		S	231	258
		S	231	256
		S	231	256
		S	231	210
		S	231	239
Schumacher, Douglas	Hill Top Research, Inc. 1275 Olentangy Road, Suite 202 Columbus, OH 43212	P	231	273
		S	231	209
		S	231	256
		S	231	229

**TABLE 3 (Cont.)**  
**Attachment to Form FDA 3454 for Studies 230 and 231**  
**Certification: Financial Interests and Arrangements of Clinical Investigators**

Investigator	Mailing Address	P = Principal S = Subinvestigator	Study	Site
		S	231	234
Smith, David H.G.	Memorial Research Medical Clinic 2865 Atlantic Avenue, Suite 227 Long Beach, CA 90806	P	231	202
Smith, L. Kent	Arizona Heart Institute and Foundation 2632 North 20 <sup>th</sup> Street Phoenix, AZ 85006	P	231	228
		S	231	272
Snyder, James W.	University of Nevada School of Medicine 1707 West Charleston, Suite 230 Las Vegas, NV 89102	P	231	275
		S	231	217
		S	231	226
		S	231	270
		S	231	215
		S	231	267
		S	231	215

**TABLE 3 (Cont.)**  
**Attachment to Form FDA 3454 for Studies 230 and 231**  
**Certification: Financial Interests and Arrangements of Clinical Investigators**

Investigator	Mailing Address	P = Principal S = Subinvestigator	Study	Site
		S	231	205
		S	231	269
		S	231	267
		S	231	239
Stuccio-White, Nina	ICSL-Clinical Studies 100 Brick Road, Suite 315 Marlton, NJ 08053	P	231	218
		S	231	215
		S	231	218
		S	231	271
Taber, Louise	ICSL-Clinical Studies 2222 East Highland Road, Suite 225 Phoenix, AZ 85016	P	231	222
		S	231	218
		S	231	228

**TABLE 3 (Cont.)**  
**Attachment to Form FDA 3454 for Studies 230 and 231**  
**Certification: Financial Interests and Arrangements of Clinical Investigators**

Investigator	Mailing Address	P = Principal S = Subinvestigator	Study	Site
		S	231	268
Tonkon, Melvin	Anaheim Heart and Research Institute 1211 West La Palma, Suite 207 Anaheim, CA 9801	P	231	204
		S	231	245
Truitt, Timothy S.	Health Advance Institute 2202 South Babcock Street, Suite 101 Melbourne, FL 32901	P	231	206
		S	231	201
Vizari, Nostratola D.	University of California Irvine Medical Center 101 City Drive South Building 53, Rte. 81 Orange, CA 92868	P	231	220
Vogelbach, Heimer	Huntington Memorial Hospital Department of Cardiology 100 West California Boulevard Pasadena, CA 91105	P	231	270
		S	231	207
		S	231	246
		S	231	204
Weschler, Jonathan	ICSL-Clinical Studies 2931 North Tenaya Way, Suite 102 Las Vegas, NV 89128	P	231	208
		S	231	245

**TABLE 3 (Cont.)**  
**Attachment to Form FDA 3454 for Studies 230 and 231**  
**Certification: Financial Interests and Arrangements of Clinical Investigators**

Investigator	Mailing Address	P = Principal S = Subinvestigator	Study	Site
Williams, Kenneth	1120 North Rolling Road Baltimore, MD 21228	P	231	226
		S	231	245
		S	231	204
		S	231	256
		S	231	256
		S	231	268
		S	231	245
Wofford, Marion	University of Mississippi Medical Center, Division of Hypertension 2500 North State Street Jackson, MS 39216-4505	P	231	269
Wojnowich, Leonard	KCSL-Clinical Studies 6065 Roswell, Suite 820 Atlanta, GA 30328	P	231	246
		S	231	216
		S	231	268
		S	231	205

**TABLE 3 (Cont.)**  
**Attachment to Form FDA 3454 for Studies 230 and 231**  
**Certification: Financial Interests and Arrangements of Clinical Investigators**

Investigator	Mailing Address	P = Principal S = Subinvestigator	Study	Site
		S	231	269
		S	231	229
		S	231	229
		S	231	204
		S	231	270
		S	231	237

5/17/02

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

### **BACKGROUND**

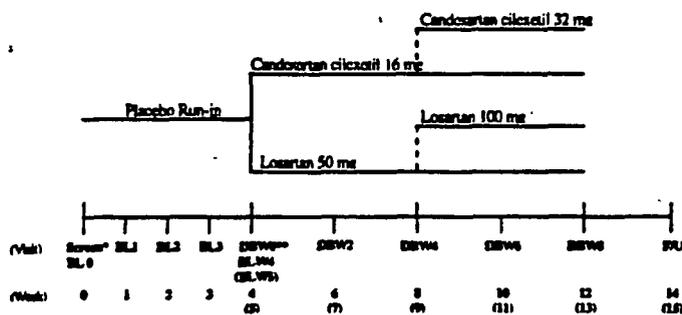
On 9/27/2001 AstraZeneca submitted a supplement to their approved NDA for Candesartan cilexetil to add statements in the **Clinical Trials, Clinical Pharmacology and Overdose** sections of the labeling. They propose incorporating the results of studies 230 and 231 (the CLAIM studies) to provide comparative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

### **COMPARATIVE EFFICACY**

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

### A. The CANDLE Study

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



BL=Baseline Week, DBW=Double Blind Week  
 \* Screen/Baseline Week 0 visit allows for patients to be withdrawn from other activities prior to enrolling study  
 \*\* Double Blind Week 0 = Qualifier/Randomization Visit (Baseline Week 4 or optional Baseline)

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

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

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

The schedule of procedures was:

Study Procedures by Visit

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

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

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

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

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

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

Baseline characteristics of those randomized was:

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

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

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

### Efficacy Results

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

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

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

Subgroup analyses of the primary endpoint results were:

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

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

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

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

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

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

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

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

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

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

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

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

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

Safety Results

No deaths occurred in this study.

Patients who withdrew for adverse events were detailed as follows:

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

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

Other serious adverse events were:

Serious Adverse Events in Randomized Patients

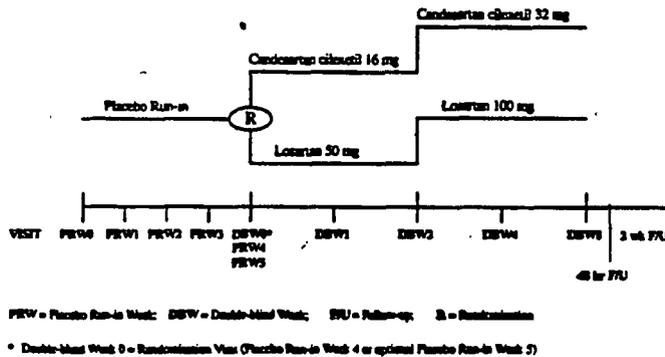
Patient	Treatment Group	Dose	Preferred Term	Days on Treatment
008/005	Candesartan cilexetil	16 mg	Myocardial Infarction	2
010/012	Losartan	100 mg	Squamous Cell Carcinoma	42
019/011	Losartan	100 mg	Dyspnea	56
034/005	Losartan	50 mg 50 mg	Ketosis Pyelonephritis	26 49
036/012	Losartan	50 mg	Tachycardia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

The CANDLE study will be discussed with the CLAIM studies.

**B. The CLAIM Studies (Studies 230 and 231)**

Studies 230 and 231 were randomized studies comparing Candesartan to losartan for antihypertensive efficacy. Each was given at the recommended starting dose (16 mg and 50 mg respectively) once-daily for 2 weeks and force-titrated to the maximum recommended dose (32 mg and 100 mg respectively) for an additional 6 weeks. The sponsor had performed other comparative studies at these doses, e.g. the CANDLE study, but with up-titration only of inadequately responding patients. Considerable discussion of the CANDLE study and new protocols ensued. During those discussions, it was noted that selection of the "usual starting dose" was somewhat arbitrary. Studies comparing the top labeled doses of Candesartan and losartan were recommended. Additionally it was noted that losartan and Candesartan could be given twice daily, and the once-daily proposal would not test Candesartan against a BID losartan dosing regimen that provide more antihypertensive effect at the same daily dose. Finally, since the losartan used in these studies was encapsulated to maintain blinding, the sponsor needed to perform a bioequivalence study comparing the PK of the encapsulated to the nonencapsulated losartan. That has been included and the results of the PK study will be reviewed by the Biopharmaceutics reviewer.

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



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

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

The disposition of these patients was as follows:

	Candesartan Cilexetil	Losartan	Overall
Patients Entered			926
Randomized to Double-blind (Safety population)	307	304	611
Discontinued	37 (12.1%)	37 (12.2%)	74 (12.1%)
-Lost to Follow-up	5 (1.6%)	4 (1.3%)	9 (1.5%)
-Lack of Response	8 (2.6%)	13 (4.3%)	21 (3.4%)
-Adverse Event	9 (2.9%)	6 (2.0%)	15 (2.4%)
-Consent Withdrawn	10 (3.3%)	8 (2.6%)	18 (2.9%)
-Sponsor/Investigator Decision	5 (1.6%)	6 (2.0%)	11 (1.8%)
Completed Study	268 (87.9%)	267 (87.8%)	535 (87.6%)

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

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

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

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

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

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

Subgroup analyses were presented in the following chart:

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

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

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

The demographic features of these patients were:

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

Disposition of these patients was:

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

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

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

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

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

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

Subgroup analyses were presented as follows:

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

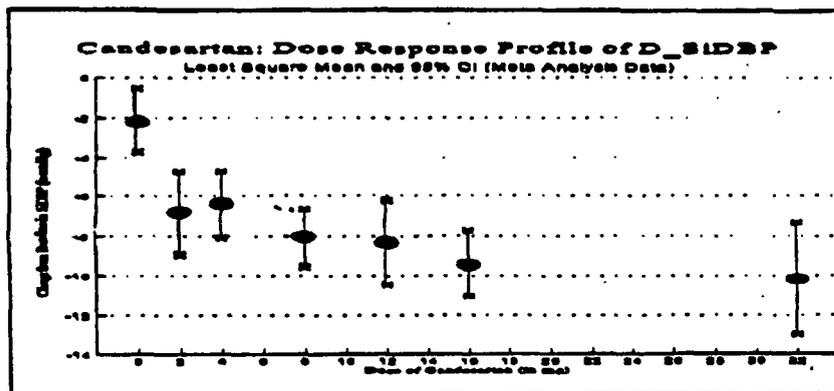
Concerning safety no deaths occurred. There were 4 serious adverse events reported; 3 in the Candesartan group (cardiac failure, myocardial infarction and accident and/or injury), and 1 in the losartan group (colitis). 11 patients withdrew for adverse reactions; 6 in the Candesartan group and 5 in the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

### Discussion

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

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

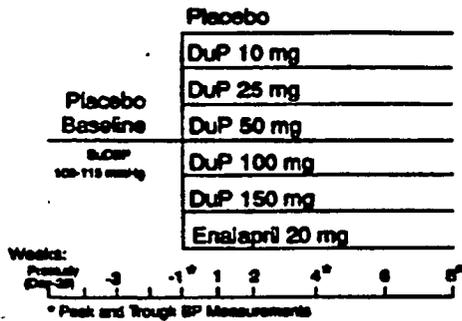
**Candesartan: Least Square Means Profile of Change From Baseline in SiDBP  
All Studies in the Meta Analysis Data**



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

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

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



DuP was losartan.  
The results were displayed in the review:

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

Treatment	N	Baseline			Treatment			Change			Comparison					
		Mean	S.D.		Mean	S.D.		Mean	S.D.	Adj Mean	vs. B	vs. C	vs. D	vs. E	vs. F	vs. G
Placebo (A)	78	103.5	3.8		97.8	8.8	-5.6	7.8	-3.3		*	NS	**	**	**	**
LOS 10 (B)	80	104.3	3.9		96.3	9.7	-7.9	7.6	-7.8		-	NS	*	NS	NS	**
LOS 25 (C)	82	103.3	3.7		96.3	9.3	-6.8	7.9	-6.4		-	-	**	**	**	**
LOS 50 (D)	78	104.1	3.7		94	8.3	-10.1	7	-10.1		-	-	-	NS	NS	NS
LOS 100 (E)	89	104.1	4.3		94.2	8	-9.9	6.9	-9.9		-	-	-	-	NS	NS
LOS 150 (F)	84	103.4	3.4		93.7	9.4	-9.7	8	-9.5		-	-	-	-	-	NS
ENAL 20 (G)	82	103.1	3.8		91.9	8.2	-11.2	6.7	-10.8		-	-	-	-	-	-

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

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

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

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

Treatment	N	Baseline			Treatment			Change			Comparison			
		Mean	Median	S.D.	Mean	Median	S.D.	Mean	Median	S.D.	Adj Mean	vs. B	vs. C	vs. D
Placebo (A)	102	101.3	99.0	3.1	99.3	98.5	9.8	-2.0	-2.5	8.4	-2.1	**	**	**
Losartan 25 qd (B)	105	101.8	100.0	3.5	96.0	93.0	8.4	-3.8	-6.0	6.7	-3.9	-	NS	*
Losartan 50 qd (C)	101	102.3	100.0	6.3	96.0	93.0	9.3	-4.3	-7.0	7.4	-6.6	-	-	NS
Losartan 25 bid (D)	101	102.0	101.0	5.3	94.0	93.0	8.8	-8.0	-8.0	7.9	-8.3	-	-	-

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

\*\* - TREATMENT DIFFERENCE STATISTICALLY SIGNIFICANT, P<0.01

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

For Candesartan, no study of the drug given in divided doses was provided. The approved labeling states: "With once-daily dosing, blood pressure effect was maintained over 24 hours, with trough-to-peak ratios of blood pressure effect generally over 80%."

AstraZeneca did provide a study comparing the antihypertensive effects of CC 8 and 16 mg to losartan 50 mg and placebo, each given once-daily. Results of that study per the sponsor follows:

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

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

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

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

For losartan that section states:

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

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

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

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

**STUDY 230**

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

**STUDY 231**

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

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

Study 230:

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

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

Study 231:

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

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

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

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

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

Treatment		Baseline	DB Wk 2	DB Wk 4	DB Wk 6	DB Wk 8	DB Wk 8 (LOCF)
Not Up-titrated							
Candesartan cilexetil 16 mg	N	75	75	72	73	71	75
	Mean	98.4	87.0	83.9	84.1	85.6	85.8
	SD	2.5	6.9	5.4	6.7	7.0	7.0
Losartan 50 mg	N	74	73	70	66	64	74
	Mean	99.1	89.7	84.2	84.4	86.2	87.8
	SD	3.3	9.2	6.4	6.2	6.4	9.0
Up-titrated							
Candesartan cilexetil 16, 32 mg	N	85	85	85	84	84	85
	Mean	102.1	95.3	96.8	91.5	92.3	92.4
	SD	4.7	7.6	5.3	7.6	7.7	7.7
Losartan 50, 100 mg	N	95	95	95	95	93	95
	Mean	101.6	96.4	97.7	93.8	94.2	94.4
	SD	4.4	7.8	5.5	7.7	8.3	8.4

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

The results of the CLAIM studies as well as the CANDLE study do support the conclusion that 16 mg CC once-daily provides more antihypertensive effect than losartan 50 mg given once-daily. Higher doses did not provide more antihypertensive effect than the usual starting doses in the ITT analyses. That finding is consistent with the data from the original NDAs. Suggestions that the 32 mg dose once-daily of Candesartan might be superior to 100 mg of losartan once-daily in patients not adequately responding to the usual starting doses would need to be studied in a properly designed trial.

Since the CANDLE study demonstrated that once-daily 16 mg of Candesartan and 50 mg of losartan provided similar percentages of adequately controlled patients after 2 weeks (46% and 42% respectively), the clinical superiority of one drug over the other was not evident.

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

"Two identically designed, concurrently conducted, 8 week, multicenter, double-blind, randomized, forced-titration studies were performed to compare the antihypertensive efficacy of candesartan cilexetil and losartan at their once-daily maximum doses.

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

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

## HEPATICALLY IMPAIRED PATIENTS

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

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

The PK results for day 1 were:

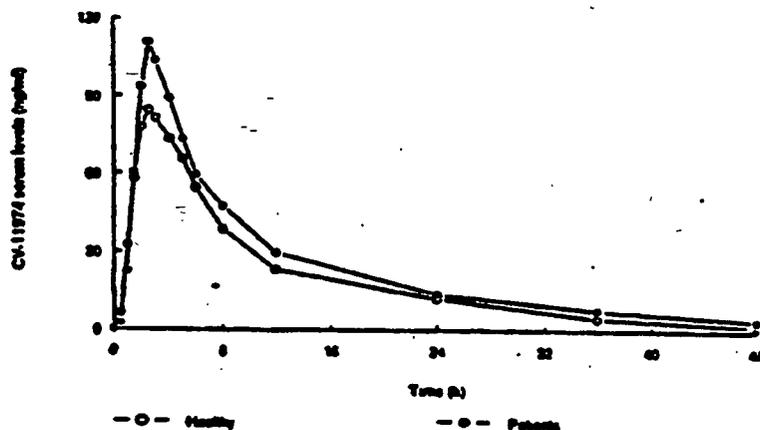
	Arithmetic				Geometric			
	Mean	SD	95% C.I. of the mean lower - upper	Median	75% percentile	Mean	SD	95% C.I. of the mean lower - upper
T <sub>1/2</sub> (h)	12	5.3	6.4 - 15	10.5	14	99	49.1	67.1 - 137
C <sub>max</sub> (ng/ml)	2.7	0.85	2.3-3.9	2.5	3.0	661	234	606 - 1112
T <sub>max</sub> (h)						1030	483	776 - 1367
AUC <sub>0-∞</sub> (ng·h/ml)						1167	560	918 - 1499
AUC <sub>0-t</sub> (ng·h/ml)*								
MRT <sub>0-∞</sub> (h)								

\* t = timepoint of last measurable concentration above blq

### HEALTHY VOLUNTEERS

	Arithmetic				Geometric			
	Mean	SD	95% C.I. of the mean lower - upper	Median	75% percentile	Mean	SD	95% C.I. of the mean lower - upper
T <sub>1/2</sub> (h)	3.3	2.7	2.5 - 11	3.4	11	95.2	29.9	78.4 - 116
C <sub>max</sub> (ng/ml)	3.8	1.4	2.7-3.9	3.5	3.2	708	214	641 - 927
T <sub>max</sub> (h)						864	284	703 - 1062
AUC <sub>0-∞</sub> (ng·h/ml)						909	307	737 - 1129
AUC <sub>0-t</sub> (ng·h/ml)*								
MRT <sub>0-∞</sub> (h)								

\* t = timepoint of last measurable concentration above blq



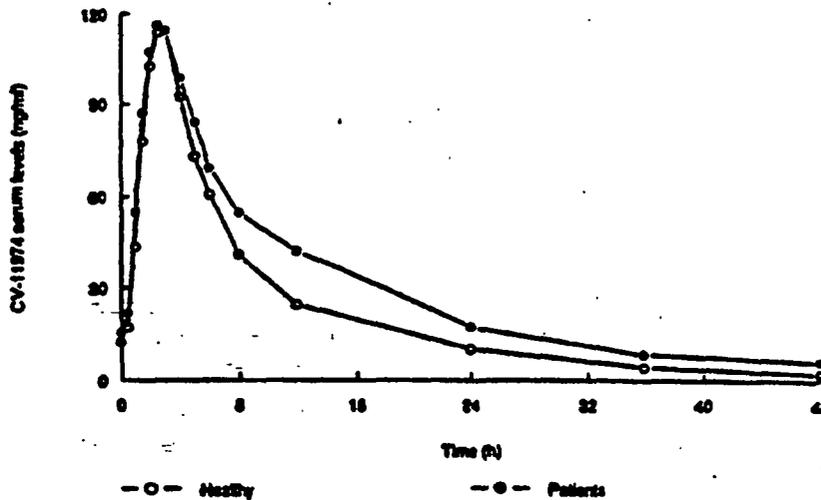
Results for day 7 were:

**LIVER IMPAIRED PATIENTS**

	Arithmetic					Geometric		
	Mean	SD	95% C.I. of the mean lower - upper	Median	75% percentile	Mean	SD	95% C.I. of the mean lower - upper
T <sub>1/2</sub> (h)	17	4.3	8.5 - 18	10	15			
C <sub>max</sub> (ng/ml)	15.4	13.8	0.88 - 24.1	14.1	19.4	112	60.2	35.3 - 147
C <sub>min</sub> (ng/ml)						45.3	18.9	35.1 - 66.4
T <sub>1/2</sub> (h)	2.8	1.1	2.2 - 3.6	2.5	3.3			
T <sub>1/2</sub> (actual)								
AUC <sub>0-∞</sub> (ng·h/ml)						1060	456	634 - 1399
R <sub>ac</sub>						1.0	0.31	0.80 - 1.2
PTP						2.1	1.0	1.6 - 2.8
PTS						7.7	17	3.7 - 46
MRT <sub>0-∞</sub> (h)						17	7.6	10 - 34

**HEALTHY VOLUNTEERS**

	Arithmetic					Geometric		
	Mean	SD	95% C.I. of the mean lower - upper	Median	75% percentile	Mean	SD	95% C.I. of the mean lower - upper
T <sub>1/2</sub> (h)	10	2.1	6.3 - 11	10	11			
C <sub>max</sub> (ng/ml)	12.3	8.12	2.83 - 25.5	11.1	16.0	116	31.2	66.0 - 137
C <sub>min</sub> (ng/ml)						36.9	6.48	32.0 - 42.6
T <sub>1/2</sub> (h)	2.6	0.36	2.4 - 2.8	2.5	3.0			
T <sub>1/2</sub> (actual)								
AUC <sub>0-∞</sub> (ng·h/ml)						680	205	760 - 1018
R <sub>ac</sub>						1.0	0.36	0.8 - 1.2
PTP						2.8	0.47	2.5 - 3.1
PTS						9.2	6.0	6.7 - 13
MRT <sub>0-∞</sub> (h)						10	1.3	9.3 - 11



Unbound fraction results for days 1 and 7 were:

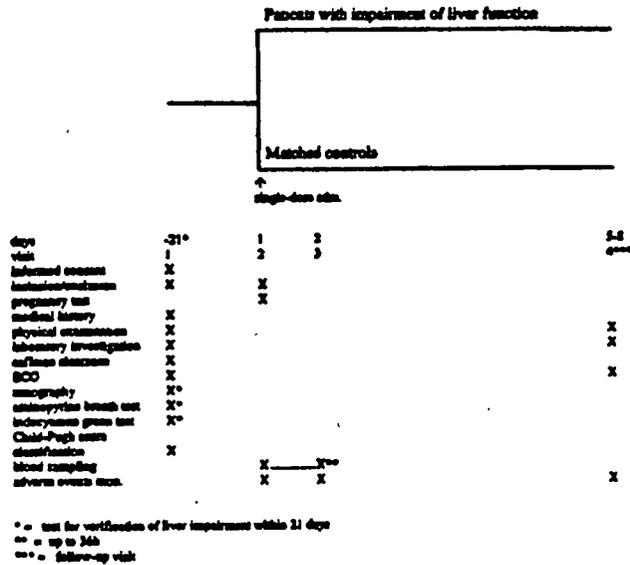
**UNBOUND CV-11974 IN SERUM IN % OF TOTAL AMOUNT OF CV-11974**

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

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

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

The design of the study was:



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

Table 9.4.3:1 Child-Pugh score classification

	1 point	2 points	3 points
Albumin (g%)	>3.5	2.8-3.5	<2.8
Total Bilirubin (mg%)	<2.0	2.0-3.0	>3.0
Quick-test (PT) (%)*	>70	40-70	<60
Ascites	no	moderate	severe
Encephalopathy	no	I-II	III-IV

Child-Pugh A: 3-6 points, Child-Pugh B: 7-9 points, Child-Pugh C: 10-15. Child-Pugh C patients were not included in the study due to the severity of their disease.

\* % of normal values

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

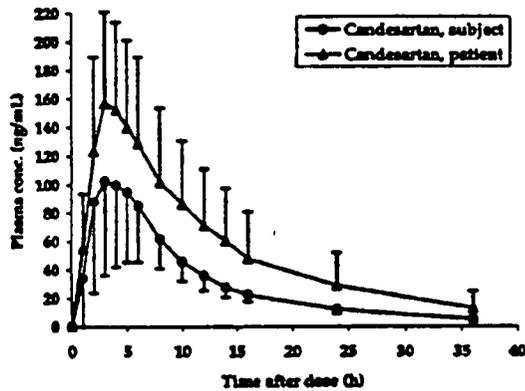
The major PK analytic results were:

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

Parameters	Group	Estimate	95% CI	
			Lower	Upper
$AUC_{0-\infty}$ (ng <sup>2</sup> /h/mL)	Patients	2021	1490	2739
	Healthy volunteers	1135	900	1430
$C_{max}$ (ng/mL)	Patients	156	116	208
	Healthy volunteers	95	65	138

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

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



Subject = healthy volunteer

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

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

Parameters	Group	Estimate	95% CI
$AUC_{0-\infty}$ (ng <sup>2</sup> /h/mL)	Patients, Child-Pugh A	1730	1160; 2578
	Matched healthy volunteers	1335	869; 2051
	Patients Child-Pugh B	2361	1327; 4200
	Matched healthy volunteers	965	745; 1250
$C_{max}$ (ng/mL)	Patients Child-Pugh A	182	122; 272
	Matched healthy volunteers	117	57; 237
	Patients Child-Pugh B	133	79; 245
	Matched healthy volunteers	77	48; 122

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

Adverse events were reported as follows:

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

Healthy volunteers					
Run-in (n=12)	Cand. cil.	(n=12)	No drug	(n=12)	
		Headache	1	Dizziness/vertigo	1

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

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

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

\* CC = candesartan cilexetil  
 \* same patient as 1997AU01985 with additional AE reported

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

### Discussion

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

## OVERDOSAGE

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

**Cases of Overdose with Candesartan Cilexetil**

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

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

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

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

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

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

## **CONCLUSIONS AND RECOMMENDATIONS**

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

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

Other suggested modifying language that might be included is:

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

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

CC: Dr. Throckmorton  
Dr. Stockbridge  
Dr. Nhi Nguyen  
Dr. Hung  
Mr. Fromm

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/s/

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Stephan Fredd  
5/17/02 07:27:21 AM  
MEDICAL OFFICER

Safety Update Review

There have been no safety updates since the original submission of September 27, 2001.

APPEARS THIS WAY  
ON ORIGINAL



Douglas C. Throckmorton, M.D.  
Division of Cardio-Renal Drug Products, HFD-110

Food and Drug Administration  
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### Memorandum

**DATE:** 7.22.02

**FROM:** Douglas C. Throckmorton, M.D., Director  
Division of Cardio-Renal Drug Products (DCRDP), HFD-110

**SUBJECT:** NDA 20-838/S015,  
**NAME OF DRUG:** Candesartan Cilexetil  
**SPONSOR:** AstraZeneca LP

#### DOCUMENTS USED FOR MEMO:

1. Medical Review by Stephen Fredd, M.D., dated 5.17.02.
2. Statistical Review by H.M. James Hung, Ph.D., 5.17.02.
3. Biopharmaceutics Review by B. Nhi Nguyen, Ph.D., dated 5.1.02.
4. AstraZeneca Presentation Slides for Advisory Committee, July 18, 2002.

#### CONCLUSIONS

This memorandum constitutes the secondary review for the named supplement as well as the Divisional memorandum for its approvability, and a recommendation for the description of candesartan as superior in reducing blood pressure (BP) when used at maximal approved dose in comparison with losartan when used at the maximal approved dose. Additional language is recommended to reflect a prolonged AUC for candesartan seen in patients with moderate hepatic impairment.

#### BACKGROUND

The sponsor has been in discussions with the Agency about assessing superior efficacy for candesartan when compared with losartan since shortly after candesartan approval in 1998. A timeline for these discussions was provided by the sponsor in their presentation to the Advisory Committee (Regulatory section). Ultimately, the Division enunciated the need for replicated measurement of comparative antihypertensive effect for the top approved doses of the two drugs in order to assess the claim of superiority. The results of the sponsor's response to this need were submitted in this supplement, and resulted in the recently-completed Advisory Committee.

#### CHEMISTRY

There was no Chemistry review of this supplement and no issues identified.

#### PHARMACOLOGY TOXICOLOGY

There was no Pharmacology-Toxicology review of this supplement and no issues identified.

### CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

The Biopharmaceutics review by Dr. Nguyen contains two items:

- A review of study SH-AHC-0015 assessing the bioequivalence of the commercially available losartan potassium 50 mg tablet with the same losartan potassium 50 mg tablet in a gelatin capsule. The latter form was needed to conduct the clinical trials submitted in support of the superiority claim (see Dr. Fredd's review).
- A review of study SH-AHC-0009 examining the pharmacokinetics of candesartan in patients with hepatic impairment. The currently approved label for candesartan has the following information about the use of candesartan in patients with hepatic impairment:
  - No differences in the pharmacokinetics of candesartan were observed in patients with mild to moderate 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).

There were no biopharmaceutics data collected in the trials comparing the antihypertensive efficacy of candesartan and losartan.

Regarding the bioequivalence study, the experimental formulation (encapsulation) did not affect the pharmacokinetics of the losartan significantly, and the two formulations were considered bioequivalent (see Dr. Nguyen's review, page 2, table 2 for results).

Regarding the study in patients with hepatic impairment, six patients with mild and six with moderate hepatic impairment (assessed by Child Pugh score) received a single dose of candesartan 16 mg. The pharmacokinetic profile of candesartan in these patients was compared with 6 healthy controls matched for age, gender and weight. The patients with hepatic impairment had a 78% increase in AUC and a 65% increase in C<sub>max</sub> compared with healthy controls (both comparisons statistically significant). When further separated into patients with mild and moderate degrees of hepatic impairment, the largest changes in kinetics were seen in the patients with moderate impairment: 145% increase in AUC and 73% increase in C<sub>max</sub> compared with healthy subjects (see page 3, table 4). No significant difference in the half-life was observed between any of the treatment groups. According to the approved candesartan label, its kinetics are linear over the dose-range studied. No dose-dependent adverse events were identified in this study (this is, of course, to be expected).

The Office of Clinical Pharmacology and Biopharmaceutics has proposed language recommending a lower initial dose for patients with moderate hepatic impairment, with no dosage change recommended for patients with mild hepatic disease (see page 3-4). I concur with this recommendation, as the expected increase in AUC for patients with moderate disease is sufficient to bring their serum levels to the next higher dose (that is, administration of 16 mg will yield serum AUC equivalent to 32 mg). This recommendation is not strongly held, as these drugs have no identified dose-dependent adverse effects.

### MEDICAL/STATISTICAL REVIEW

Both Dr. Fredd and Hung concluded that candesartan at 32 mg had significantly greater antihypertensive efficacy than did losartan 100 mg per day in the two trials of most interest (protocols 230 and 231). Both reviewers also comment on the fact that the majority of the changes in blood pressure during both trials occurred at doses lower than 32 mg (see Dr. Hung's review table 231-2 for a summary). Dr. Fredd's conclusion from this is that one cannot infer superiority of candesartan 32 mg to losartan 100 mg, although his rationale is not clear to me. Part of the argument is a belief, which I share, that it would be a stronger case for superiority if it could be shown at each of the approved doses of candesartan. Over the course of the trial, however, Dr. Hung pointed out that the trend at all doses favored candesartan (see page 11 of his review). Another part of Dr. Fredd's concerns may have been his belief that this finding (most of the changes occurred at lower doses) limit the utility of the directions we give to patients (titration to top dose). Again, I have some sympathy for this position, as it seems clear that our directions are not often followed by practicing physicians. However, the trial was conducted as we suggested it be done, and was intended to not to inform individual physician behavior, but rather to describe the effects of the relevant (highest approved) doses of candesartan and losartan on BP lowering. In this regard, the results are clear: in the two pivotal trials (230 and 231) the regimen of candesartan 16 mg force-titrated to 32 mg lowered BP by 1 to 2.2 mmHg diastolic and 3.5 mmHg more than did losartan 50 mg force-titrated to 100 mg.

There is one other issue, relating to the absence of a BID dosing regimen for both candesartan and losartan. Dr. Fredd reviewed the relevant data for losartan (see page 14 of his review). In a relatively large trial (one hundred plus people per dose) no significant difference between losartan 25 mg BID and 50 mg qD was observed (the difference between the two mean reductions was 1.7 mm Hg diastolic with the larger reduction with losartan 25 mg BID). Reassurance is also to be found in the observation that at peak effect candesartan was also superior to enalapril (see Dr. Hung's review, page 7). Two points to make: first, I agree with the view of the Advisory Committee. If there is a significant difference favoring the BID dose, it can't be a 'fair' comparison to use the qD dosing (this was not seen here despite a largish trial examining the issue). You correctly point out that we would label that drug as BID and not qD. Second, if a drug's evaluation does not adequately evaluate the consequences of BID dosing, say by underpowering the study, the sponsor will bear a risk of their pharmacokinetics being used against them by another sponsor.

Does comparatively greater BP lowering matter? Simply, we have no reason to believe otherwise. Are there safety concerns for candesartan that undermine the relevance of this finding when compared with losartan? Absolutely not (certainly nothing found in the safety reviews of these trials and nothing reported in the two labels suggests it).

#### Pediatrics

A Written Request for candesartan has been issued for the treatment of pediatric hypertension.

#### SUMMARY

I concur with the recommendations of the Advisory Committee: the label for candesartan should be changed to reflect the results from the 230 and 231 trials, supporting greater antihypertensive effect for candesartan at the top approved dose when compared with top approved once daily dose of losartan. The label should include the numerical difference in BP that was observed in the two pivotal trials, as well as a clear description of the trial as comparing once per day dosing to test relative antihypertensive efficacy. Finally, the recommendations of the Biopharmaceutics reviewer regarding the consideration of a lower starting dose for patients with moderate hepatic insufficiency.

How much emphasis should be placed on the other clinical efficacy demonstrated for losartan? Provided that the label sufficiently identifies the effect as limited to a comparative antihypertensive claim (that is, the trial looked at BP, not other effects of the two drugs, such as the renal protective effects of losartan) I don't believe a statement needs to be added about what the trial did not study (e.g., renal protection in diabetes). Others in the Division have strong opinions to the contrary (Dr. Stockbridge and Karkowsky). Their concern, as I understand it, is that the interpretation of a comparison between two drugs (lowering BP in this case) is very difficult to do given the complicated and various effects the two drugs might have. Given this complexity, the surrogate of BP lowering is less likely to adequately predict greater clinical benefit than would be the case for a placebo-controlled trial, and is simply too 'one-dimensional' to be useful. It does seem quite important to specify that this benefit is quite focused in its meaning and under some circumstances place additional language about the clinical benefits of the comparator into the label. While I don't favor it in this case, an argument could be made to include the effects of losartan that are not felt to be related to BP lowering into the label, to prevent any misunderstanding on the part of clinicians. We are in uncharted waters there, and a broader discussion of such labeling within the Center would be useful.

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Doug Throckmorton  
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