DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-093/S-004

AstraZeneca LP
Attention: Ms. Cindy Lancaster
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803-8355

Dear Ms. Lancaster:

Please refer to your supplemental new drug application dated 24 June 2004, received 25 June 2005, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Atacand® (candesartan cilexetil) 16-12.5 and 32-12.5 mg Tablets.

We acknowledge receipt of your submission dated 24 June 2004 which constituted a complete response to our 11 December 2003 approvable letter and our 7 October 2002 supplement request letter.

This supplemental new drug application provides for electronic final printed labeling revised as follows:

1. **DESCRIPTION**, 2nd paragraph, the chemical name of candesartan cilexetil has been changed to:

   (±)-1-Hydroxyethyl 2-ethoxy-1-[*p*-(*o*-1*H*-tetrazol-5-yl-phenyl)benzy1]-7-benzimidazolecarboxylate, cyclohexyl carbonate (ester).

2. **Clinical Pharmacology, Special Populations**, *Hepatic Insufficiency* has been revised as follows:

   The first sentence stating **(b)(4)** was deleted and replaced with the following paragraph:

   The pharmacokinetics of candesartan were compared in patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment to matched healthy volunteers following a single dose of 16 mg candesartan cilexetil. The AUC for candesartan in patients with mild and moderate hepatic impairment was increased 30% and 145% respectively. The C_{max} for candesartan was increased 56% and 73% respectively. The pharmacokinetics of candesartan in severe hepatic impairment have not been studied. No dose adjustment is recommended for patients with mild hepatic impairment. In patients with moderate hepatic impairment, consideration should be given to initiation of ATACAND at a lower dose, such as 8 mg. If a lower starting dose is selected for candesartan cilexetil, ATACAND HCT is not recommended for initial titration because the appropriate initial starting dose of candesartan cilexetil cannot be given. (See **DOSAGE AND ADMINISTRATION**).

3. **Under Carcinogenesis, Mutagenesis, Impairment of Fertility,** revisions included the following:

   The subheading **(b)(4)** was deleted and the subsection text that deals with genetic toxicological studies was revised as follows:

Candesartan cilexetil or candesartan (the active metabolite), in combination with hydrochlorothiazide, tested positive *in vitro* in the Chinese hamster lung (CHL) chromosomal aberration assay and mouse lymphoma mutagenicity assay. The candesartan cilexetil/hydrochlorothiazide combination tested negative for mutagenicity in bacteria (Ames test), for unscheduled DNA synthesis in rat liver, for chromosomal aberrations in rat bone marrow and for micronuclei in mouse bone marrow.

Both candesartan and its O-deethyl metabolite tested positive for genotoxicity in the *in vitro* CHL chromosomal aberration assay. Neither compound tested positive in the Ames microbial mutagenesis assay or in the *in vitro* mouse lymphoma cell assay. Candesartan (but not its O-deethyl metabolite) was also evaluated *in vivo* in the mouse micronucleus test and *in vitro* in the Chinese hamster ovary (CHO) gene mutation assay, in both cases with negative results. Candesartan cilexetil was evaluated in the Ames test, the *in vitro* mouse lymphoma cell assay, the *in vivo* rat hepatocyte unscheduled DNA synthesis assay and the *in vivo* mouse micronucleus test, in each case with negative results. Candesartan cilexetil was not evaluated in the CHL chromosomal aberration or CHO gene mutation assays.

When hydrochlorothiazide was tested alone, positive results were obtained *in vitro* in the CHO sister chromatid exchange (clastogenicity) and mouse lymphoma cell (mutagenicity) assays and in the *Aspergillus nidulans* non-disjunciton assay. Hydrochorothiazide was not genotoxic *in vitro* in the Ames test for point mutations and the CHO test for chromosomal aberrations, or *in vivo* in assays using mouse germinal cell chromosomes, Chinese hamster bone marrow chromosomes, and the Drosophila sex-linked recessive lethal trait gene.

4. Under **PRECAUTIONS, Geriatric Use**, the following sentence was added as a separate paragraph:

Hydrochlorothiazide is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function.

5. Under **DOSAGE AND ADMINISTRATION, Patients with Hepatic Impairment,** the following paragraph was inserted:

The usual regimens of therapy with ATACAND HCT may be followed in patients with mild hepatic impairment. In patients with moderate hepatic impairment, consideration should be given to initiation of ATACAND at a lower dose, such as 8 mg. If a lower starting dose is selected for candesartan cilexetil, ATACAND HCT is not recommended for initial titration because the appropriate initial starting dose of candesartan cilexetil cannot be given. (See **CLINICAL PHARMACOLOGY, Special Populations,** *Hepatic Insufficiency*).

6. Minor revisions were noted wherever Candesartan Cilexetil appears as a subheading, it has been revised to be consistent throughout the label and appears as *Candesartan Cilexetil*, not *Candesartan cilexetil*.

7. Under the **Post-Marketing Experience** subsection, the following was inserted per the supplement request letter dated 11 December 2004:

"Rare reports of rhabdomyolysis have been reported in patients receiving angiotensin II receptor blockers." However, the word "reports" was substituted for the word **(b)(4)**.

We completed our review of this supplemental new drug application, It is approved, effective on the date of this letter, for use as recommended in the final printed labeling (FPL) submitted on 24 June 2004.

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions please call:

Cheryl Ann Borden, MSN, R.N., CCRN, CCNS
Regulatory Health Project Manager
(301) 594 5312.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., PhD
Acting Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Norman Stockbridge

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