

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER**

**20-838/S-015**

**Approval Letter(s)**



NDA 20-838/S-015

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

Dear Ms. Lancaster:

Please refer to your supplemental new drug application dated September 27, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Atacand (candesartan cilexetil) Tablets, 4, 8, 16, and 32 mg.

We acknowledge receipt of your submissions dated August 1, 7, and 22, and September 3, 2002. Your submission of September 3, 2002 constituted a complete response to our July 26, 2002 approvable letter.

This supplemental new drug application provides data on the comparison of the antihypertensive effects of Atacand (candesartan cilexetil) Tablets and Cozaar (losartan potassium) Tablets. It also proposes revisions to the **CLINICAL PHARMACOLOGY, (Clinical Trials & Special Populations), PRECAUTIONS, OVERDOSAGE, and DOSAGE AND ADMINISTRATION** sections of the labeling.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the submitted electronic final printed labeling (package insert included in your submission of September 3, 2002). Accordingly, the supplemental application is approved effective on the date of this letter.

Please make the following change to the labeling at your next printing:

Under **DESCRIPTION**, 2<sup>nd</sup> paragraph, please change the chemical name of candesartan cilexetil to:

(+)-1-Hydroxyethyl 2-ethoxy-1-[p-(*o*-1*H*-tetrazol-5-ylphenyl)benzyl]-7-benzimidazolecarboxylate, cyclohexyl carbonate (ester).

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Cardio-Renal Drug Products and two copies of both the promotional materials and the package insert directly to:

---

Food and Drug Administration  
Rockville MD 20857

Division of Drug Marketing, Advertising, and Communications, HFD-42  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, Maryland 20857

Please submit one market package of the drug product when it is available.

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 contact:

Mr. Edward Fromm  
Regulatory Health Project Manager  
(301) 594-5332

Sincerely,

*(See appended electronic signature page)*

Robert Temple, M.D.  
Director  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

Enclosed Labeling Text

-----  
**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
-----

/s/

-----  
Robert Temple  
9/13/02 03:20:12 PM

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER**

**20-838/S-015**

**Approvable Letter**



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 20-838/S-015

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

Dear Ms. Lancaster:

Please refer to your supplemental new drug application dated September 27, 2001, received September 27, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Atacand (candesartan cilexetil) Tablets, 4, 8, 16, and 32 mg.

We acknowledge receipt of your submissions dated March 26, April 4, 12, and 23, May 15, June 4, 6, 10, and 17, July 2, 8, 17, and 19, 2002.

This supplemental new drug application provides data on the comparison of the antihypertensive effects of Atacand (candesartan cilexetil) Tablets and Cozaar (losartan potassium) Tablets. It also proposes revisions to the **CLINICAL PHARMACOLOGY (Clinical Trials & Special Populations)**, **PRECAUTIONS (General)**, **OVERDOSAGE**, and **DOSAGE AND ADMINISTRATION** sections of the labeling.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to submit final printed labeling revised as follows:

1. Under **CLINICAL PHARMACOLOGY, Clinical Trials**, the 2<sup>nd</sup> paragraph should be changed to:

The antihypertensive effects of candesartan cilexetil and losartan potassium at their highest recommended doses administered once per day were compared in two randomized, double-blind trials. In a total of xxx subjects with mild to moderate hypertension who were not receiving other antihypertensive therapy, candesartan cilexetil 32 mg lowered systolic and diastolic blood pressure by 2 to 3 mmHg on average compared with losartan potassium 100 mg, when measured at the time of either peak or trough effect. The antihypertensive effects of twice daily dosing of either candesartan or losartan were not studied.

2. Under **PRECAUTIONS**, the 2<sup>nd</sup> paragraph of the *Carcinogenesis, Mutagenesis, Impairment of Fertility* subsection should be changed to:

Candesartan and its O-deethyl metabolite tested positive for genotoxicity in the *in vitro* Chinese hamster lung (CHL) chromosomal aberration assay. Neither compound tested positive in the Ames microbial mutagenesis assay or 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 and rat hepatocyte unscheduled DNA — assays 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 assay.

3. Please use the generic name "candesartan cilexetil" throughout the labeling where appropriate.

In addition, all previous revisions as reflected in the most recently approved labeling must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL, ten of which individually mounted on heavy weight paper or similar material.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Cardio-Renal Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, Maryland 20857

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with these changes prior to approval of this supplemental application.

If you have any questions, please contact:

Mr. Edward Fromm  
Regulatory Project Manager  
(301) 594-5332

Sincerely,

*{See appended electronic signature page}*

Robert Temple, M.D.  
Director  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**

/s/

-----  
Robert Temple  
7/26/02 05:56:37 PM

30 pages redacted from this section of  
the approval package consisted of draft labeling