DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-888/S-035

AstraZeneca Pharmaceuticals 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 August 23, 2001 submitted under section 505(b)/pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Zestoretic (lisinopril/hydrochlorothiazide) 20/12.5, 20/25 and 10/12.5 mg Tablets.

We acknowledge receipt of your submissions dated February 3 and March 31, 2003.

This supplemental drug application provides for electronic final printed labeling (FPL) revised as follows:

1. PRECAUTIONS:
Geriatric Use

> Clinical studies of ZESTORETIC did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. In a multiple dose pharmacokinetic study in elderly versus young hypertensive patients using the lisinopril/hydrochlorothiazide combination, area under the plasma concentration time curve (AUC) increased approximately 120% for lisinopril and approximately 80% for hydrochlorothiazide in older patients.
>
> This drug 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. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection. Evaluation of the hypertensive patient should always include assessment of renal function.

2. Under **DOSAGE AND ADMINISTRATION,** the subsection *Use in the Elderly* has been deleted.

In addition, the following revisions were requested under the **Warnings/Angioedema** subsection and the **Adverse Reactions** section:

1. **Warnings/Angioedema** subsection:

   Change from: **Angioedema** (subsection heading)
   Change to: **Head and Neck Angioedema** (revised subsection heading)

2. Following the **Head and Neck Angioedema** subsection and before the paragraph entitled "Patients with a history…," add the following subsection:

   Intestinal Angioedema: Intestinal angioedema has been reported in patients treated with ACE inhibitors. These patients presented with abdominal pain (with or without nausea or vomiting); in some cases there was no prior history of facial angioedema and C-1 esterase levels were normal. The angioedema was diagnosed by procedures including abdominal CT scan or ultrasound, or at surgery, and symptoms resolved after stopping the ACE inhibitor. Intestinal angioedema should be included in the differential diagnosis of patients on ACE inhibitors presenting with abdominal pain.

3. **Adverse Reactions** section:

   Change from: In very rare cases, intestinal angioedema has been reported in post marketing experience.

   Change to: In rare cases, intestinal angioedema has been reported in post marketing experience.

We have completed our review of this supplemental new drug application, as amended, and have concluded that adequate information has been presented to demonstrate that this drug is safe and effective for use as recommended in the electronic final printed labeling submitted on March 31, 2003. Accordingly, the supplemental application is approved effective on the date of this letter.

Since issuing the Approvable Letter dated, October 30, 2002 we have noted that a description of the pharmacokinetics of lisinopril in older patients is already present in the approved label in the **Pharmacokinetics and Metabolism** section. For consistency, at the time of your next printing, remove the following sentence from the **Geriatric Use** section and insert it into the **Pharmacokinetics and Metabolism** section following the description of the kinetics of lisinopril as monotherapy in the elderly: " In a multiple dose pharmacokinetic study in elderly versus young hypertensive patients using the lisinopril/hydrochlorothiazide combination, the area under the plasma concentration time curve (AUC) increased approximately 120% for lisinopril and approximately 80% for hydrochlorothiazide in older patients."

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, HF-2
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:

Alisea Sermon, Pharm.D.
Regulatory Project Manager
(301) 594-5334

Sincerely,

{See appended electronic signature page}

Douglas C.Throckmorton, M.D.
Director
Division of Cardio-Renal Drug Products
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/

Doug Throckmorton

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