



NDA 19-777/S-043

AstraZeneca Pharmaceuticals LP  
Attn: Ms. Judy W. Firor  
1800 Concord Pike  
P.O. Box 8355  
Wilmington, DE 19803-8355

Dear Ms. Firor:

Please refer to your supplemental new drug application dated August 20, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zestril (lisinopril) 2.5, 5, 10, 20, 30 and 40 mg Tablets.

We acknowledge receipt of your submission dated November 13, 2003.

Your submission of November 13, 2003 constituted a complete response to our April 28, 2003 action letter.

This supplemental new drug application proposes the following labeling changes:

1. Under **PRECAUTIONS**, the following subsection has been added:

#### **Geriatric Use**

Clinical studies of ZESTRIL in patients with hypertension did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other clinical experience in this population 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 the ATLAS trial of ZESTRIL in patients with congestive heart failure, 1,596 (50%) were 65 and over, while 437 (14%) were 75 and over. In a clinical study of ZESTRIL in patients with myocardial infarctions 4,413 (47%) were 65 and over, while 1,656 (18%) were 75 and over. In these studies, no overall differences in safety or effectiveness were observed between elderly and younger patients, and other reported clinical experiences has not identified differences in responses between the elderly and younger patients (see CLINICAL PHARMACOLOGY – Pharmacodynamics and Clinical Effects – Heart Failure and CLINICAL PHARMACOLOGY – Pharmacodynamics and Clinical Effects – Acute Myocardial Infarction).

Other reported clinical experience has not identified differences in responses between elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Pharmacokinetic studies indicate that maximum blood levels and area under the plasma concentration time curve (AUC) are doubled in older patients (see CLINICAL PHARMACOLOGY – Pharmacokinetics and Metabolism).

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 patients with hypertension, congestive heart failure, or myocardial infarction should always include assessment of renal function (see DOSAGE AND ADMINISTRATION).

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

From:

“In general, blood pressure response and adverse experiences were similar in younger and older patients given similar doses of ZESTRIL. Pharmacokinetics studies, however, indicate that maximum blood levels and area under the plasma concentration time curve (AUC) are doubled in older patients, so that dosage adjustments should be made with particular caution.”

To:

“In general, the clinical response was similar in younger and older patients given similar doses of ZESTRIL. Pharmacokinetic studies, however indicate that maximum blood levels and area under the plasma concentration time curve (AUC) are doubled in older patients, so that dosage adjustments should be made with particular caution.”

We have completed our review of this supplemental new drug application, as amended. It is approved, effective on the date of this letter, for use as recommended in the final printed labeling (FPL) submitted on November 13, 2003.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have fulfilled the pediatric study requirement for this application.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division 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, MD 20857

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:

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

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/s/

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Doug Throckmorton  
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