Dear Mr. Best:

Please refer to your March 4, 1993 supplemental new drug applications submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Zastril (lisinopril) Tablets (NDA 19-777) and Zestoretic (lisinopril and hydrochlorothiazide) Tablets (NDA 19-888).

The supplemental applications provide for final printed labeling revised as follows:

NDA's 19-777 and 19-888

1. Addition of a new subsection under PRECAUTIONS entitled "Hemodialysis Patients" that discusses anaphylactoid reactions during hemodialysis.

2. Inclusion of "Anaphylactoid Reactions (see PRECAUTIONS, Hemodialysis Patients)" to the listing of ADVERSE REACTIONS, Body as a Whole subsection.

3. Inclusion of "photosensitivity" to the listing of ADVERSE REACTIONS, Skin subsection.

4. Revision of the symptocomplex statement by creating a new subsection under the listing of ADVERSE REACTIONS entitled "Miscellaneous."

NDA 19-888 only

5. Revision of the WARNINGS-Pregnancy-Lisinopril and Hydrochlorothiazide subsection to be consistent with the statement in the Boxed Warning regarding the use of Zestoretic during pregnancy.

In addition, the word "even," which was inadvertently omitted from the boxed warning, was added to the phrase, "ACE inhibitors can cause injury and even death to the developing fetus."

We have completed the review of these supplemental applications and they are approved.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.
Please note that while we are approving these supplemental applications for now, a class statement is being prepared to address the hemodialysis issue with ACE inhibitors you should, therefore, anticipate that we will request that this warning be revised in the near future.

Sincerely yours,

3/31/93

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I-
Center for Drug Evaluation and Research

Original NDA
HFC-130/JAllen
HFD-110
HFD-110/CSO
HFD-80
HFD-232 (with labeling)
HFD-110/GBuehler/3/17/93;3/24/93
sb/3/17/93;3/30/93
R/D: JShort/3/25/93
RWolters/3/25/93
CResnick/3/29/93
SChen/3/29/93
GBuehler for NMorgenstem

Approval Date:NDA 19-777 - 5/19/88
NDA 19-888 - 7/20/89

APPROVAL
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19777/S18

FINAL PRINTED LABELING
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19777/S18

CHEMISTRY REVIEW(S)
<table>
<thead>
<tr>
<th>CHEMIST'S REVIEW</th>
<th>1. ORGANIZATION</th>
<th>2. NDA Number</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HFD-110</td>
<td>19-777</td>
</tr>
</tbody>
</table>

| 3. Name and Address of Applicant (City & State) | 4. Supplement(s) Number(s) Date(s) |
|                                               | S-018 4 Mar 93 |
| Zeneca Inc.                                   |                                |
| Wilmington, DE 19897                          |                                |

<table>
<thead>
<tr>
<th>5. Drug Name</th>
<th>6. Nonproprietary Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zestril</td>
<td>Lisinopril</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>7. Amendments &amp; Other (reports, etc) - Dates</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>8. Supplement Provides For: Revised Package Insert (PI).</th>
</tr>
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</table>

<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Antihypertensive</td>
<td>RX</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>11. Related IND(s)/NDA(s)/DMF(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NDA 19-558 Prinivil, Merck</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>12. Dosage Form(s)</th>
<th>13. Potency(ies)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCM</td>
<td>2.5, 5, 10, 20, 40 mg</td>
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<table>
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<tr>
<th>14. Chemical Name and Structure</th>
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<table>
<thead>
<tr>
<th>15. Records/Reports Current</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>16. Comments:</th>
</tr>
</thead>
</table>

S-018 is a "Special Supplement - Changes Being Effected." A new subsection is added under Precautions entitled "Hemodialysis Patients." Anaphylactic shock and photosensitivity are added to the Adverse Reactions section. A new subsection is added under Adverse Reactions entitled "Miscellaneous."

The changes described above are made to bring the PI into conformance with Merck's PI for Prinivil.

A typographical error has been corrected in the box warning.

The revised PI is dated 9/92.

<table>
<thead>
<tr>
<th>17. Conclusions and Recommendations:</th>
</tr>
</thead>
</table>

APPROVABLE

The technical aspects of the labeling are unchanged and remain satisfactory.

<table>
<thead>
<tr>
<th>18. Name</th>
<th>REVIEWER</th>
<th>Date Completed</th>
</tr>
</thead>
<tbody>
<tr>
<td>James H. Short</td>
<td>/S/</td>
<td>25 Mar 93</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Distribution:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Original Jacket</td>
</tr>
</tbody>
</table>

R/D Init: RWolters/3/25/93
The following changes have also been made to be in agreement with labeling changes for Prinivil effected by Merck Research Laboratories (MRL) under NDA 19-558:

- Inclusion of "photosensitivity" to the listing of ADVERSE REACTIONS occurring in 0.3% to 1.0% of patients, SKIN-subsection. Please refer to page 18 of the enclosed 3-column document.

- Revision of the symptom complex statement by creating a new subsection under the listing of ADVERSE REACTIONS occurring in 0.3% to 1.0% of patients, entitled "MISCELLANEOUS". Please refer to page 19 of the enclosed 3-column document.

In addition, we have corrected a typographical error in the boxed warning, the word "even" was inadvertently omitted from the phrase "ACE inhibitors can cause injury and even death to the developing fetus." Please refer to page 1 of the enclosed 3-column document.

If you should have any questions or concerns regarding this set of labeling changes, please do not hesitate to contact me.

Sincerely,

[Signature]

William A. Best  
Manager, Regulatory Compliance  
Drug Regulatory Affairs Department  
(302) 886-2135  
(302) 886-2822 (fax)

WAB/SLR/rmw  
Enclosures
The supplemental applications, which were submitted as "Special Supplements - Changes Being Effected," provide for the following labeling changes:

**NDAs 19-777 and 19-888**

1. Addition of a new subsection under PRECAUTIONS entitled "Hemodialysis Patients" that discusses anaphylactoid reactions during hemodialysis.

2. Inclusion of "Anaphylactoid Reactions (see PRECAUTIONS, Hemodialysis Patients)" to the listing of ADVERSE REACTIONS, Body as a Whole subsection.

3. Inclusion of "photosensitivity" to the listing of ADVERSE REACTIONS, Skin subsection.

4. Revision of the symptom complex statement by creating a new subsection under the listing of ADVERSE REACTIONS entitled "Miscellaneous."

**NDA 19-888 only**

5. Revision of the WARNINGS-Pregnancy-Lisinopril and Hydrochlorothiazide subsection to be consistent with the statement in the Boxed Warning regarding the use of Zestoretic during pregnancy.

In addition, the word "even", which was inadvertently omitted from the boxed warning statement, was added to the phrase "ACE inhibitors can cause injury and even death to the developing fetus."

The labeling from both applications was reviewed and found to be acceptable as proposed. The firm should be informed, however, that a class statement is being prepared for the Hemodialysis Warning. They should therefore anticipate a request to revise this paragraph in the not-too-distant future.

An approval letter will be prepared for Dr. Lipicky's signature. /S\n
Gary Buehler, CSO 3/25/93

Orig NDAs
HFD-110 Files
HFD-110 SBenton
HFD-111 GBuehler
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19777/S18

CORRESPONDENCE
Division of Cardio-Renal
Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
HPD No. 110, Room No. 16B-30
5600 Fishers Lane
Rockville, MD 20857

Gentlemen:

Re: ZESTRIL® (lisinopril/Stuart) Tablets
NDA 19-777
Special Supplement - Changes Being Effected

We take this opportunity to advise you of changes made to the labeling as provided for under 21 CFR 314.70(3)(c). We enclose 12 copies of final printed labeling (REV I 09/92) as Tab 1, which will be implemented into marketing and production activities beginning the week of March 8, 1993.

A 3-column review document is enclosed as Tab 2 and clearly illustrates the changes in labeling information. The left column represents the current labeling; the middle column represents the proposed changes; and the right column represents any comments or supporting statements.

We revised the labeling to address the potential development of anaphylactoid-reactions during dialysis using high-flux membrane dialyzers. These changes are a result of our continuing review of our adverse experience data base. Enclosed as Tab 3 are copies of adverse experiences reported in the literature relative to the potential development of anaphylactoid reactions during dialysis. These will serve as justification for these labeling changes. Specifically, the following changes have been made:

- Addition of a new subsection under PRECAUTIONS entitled "Hemodialysis Patients" which discusses anaphylactoid reactions during hemodialysis. Please refer to page 11 of the enclosed 3-column document.

- Inclusion of "Anaphylactoid Reactions (see PRECAUTIONS, Hemodialysis Patients)" to the listing of ADVERSE REACTIONS occurring in 0.3% to 1.0% of patients, BODY AS A WHOLE-subsection. Please refer to page 18 of the enclosed 3-column document.