CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: NDA 19777/S20

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

JUN 13 1995

NDA 19-777/S-020
19-888/S-015
S-020

Zeneca Pharmaceuticals
A Business Unit of Zeneca Inc.
Attention: Ms. Sandra J. Acquaviva
1800 Concord Pike
P.O. Box 15437
Wilmington, DE 19850-5437

Dear Ms. Acquaviva:

Please refer to your June 30, 1993 (NDA 19-777/S-020) and NDA 19-888/S-015) and October 28, 1994 (NDA 19-888/S-020) supplemental new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zestril (lisinopril) (NDA 19-777) and Zestoretic (lisinopril/hydrochlorothiazide) (NDA 19-888) Tablets.

We acknowledge receipt of your amendments dated May 18, 1995 to each application.

The supplemental applications, as amended, provide for final printed labeling incorporating the following revisions:

NDA 19-777/S-020

Revision of the first sentence of the **DESCRIPTION** section to read as follows:

> Lisinopril is an oral long-acting angiotensin converting enzyme inhibitor. Lisinopril, a synthetic peptide derivative, is chemically . . ..

NDA 19-777/S-020
NDA 19-888/S-015

Addition of the following new subsections to the **WARNINGS** section:

> **Anaphylactoid and Possibly Related Reactions:**
>
> Presumably because angiotensin-converting enzyme inhibitors affect the metabolism of eicosanoids and polypeptides, including endogenous bradykinin, patients receiving ACE inhibitors (including ZESTRIL/ZESTORETIC) may be subject to a variety of adverse reactions, some of them serious.

Anaphylactoid Reactions During Desensitization:

Two patients undergoing desensitizing treatment with hymenoptera venom while receiving ACE inhibitors sustained life-threatening anaphylactoid reactions. In the same patients, these reactions were avoided when ACE inhibitors were temporarily withheld, but they reappeared upon inadvertent rechallenge.

Anaphylactoid Reactions During Membrane Exposure:

NDA 19-777/S-020

Sudden and potentially life-threatening anaphylactoid reactions have been reported in some patients dialyzed with high-flux membranes (eg, AN69¶) and treated concomitantly with an ACE inhibitor. In such patients, dialysis must be stopped immediately, and aggressive therapy for anaphylactoid reactions be initiated. Symptoms have not been relieved by antihistamines in these situations. In these patients, consideration should be given to using a different class of antihypertensive agent. Anaphylactoid reactions have also been reported in patients undergoing low-density lipoprotein apheresis with dextran sulfate absorption (a procedure dependent upon devices not approved in the United States).

NDA 19-888/S-015

Thiazide-containing combination products are not recommended in patients with severe renal dysfunction. Sudden and potentially life-threatening anaphylactoid reactions have been reported in some patients dialyzed with high-flux membranes (e.g., AN69¶) and treated concomitantly with an ACE inhibitor. In such patients, dialysis must be stopped immediately, and aggressive therapy for anaphylactoid reactions be initiated. Symptoms have not been relieved by antihistamines in these situations. In these patients, consideration should be given to using a different class of antihypertensive agent. Anaphylactoid reactions have also been reported in patients undergoing low-density lipoprotein apheresis with dextran sulfate absorption (a procedure dependent upon devices not approved in the United States).

Relocation of the **Anaphylactoid Reactions During Membrane Exposure** subsection from the **PRECAUTIONS** section to the **WARNINGS** section.

Revision of the **Cough** subsection of the **PRECAUTIONS** section as follows:

> Presumably due to the inhibition of the degradation of endogenous bradykinin, persistent nonproductive cough has been reported with all ACE inhibitors, almost always resolving after discontinuation of therapy. ACE inhibitor-induced cough should be considered in the differential diagnosis of cough.

Revision of all references throughout the labeling to reflect the above changes.

NDA 19-888/S-020

Under **INDICATIONS AND USAGE**, addition of the following as the second paragraph in the section:

> These fixed-dose combinations are not indicated for initial therapy (see **DOSAGE AND ADMINISTRATION**).

Under **DOSAGE AND ADMINISTRATION**, changing the title to "Dose Titration Guided by Clinical Effect."

We have completed the review of these supplemental applications and have concluded that adequate information has been presented to demonstrate that the drugs are safe and effective for use as recommended in the final printed included in the May 18, 1995 submission. Accordingly, the supplemental applications are approved effective on the date of this letter.

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:

Ms. Kathleen Bongiovanni
Regulatory Health Project Manager
(301) 594-5300

Sincerely yours,

6/13/95

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19777/S20

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APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-777/S-020
19-888/S-015

SEP 23 1993

Zeneca Pharmaceuticals Group
Attention: William J. Kennedy, Ph.D.
P.O. Box 751
Wilmington, DE 19897

Dear Dr. Kennedy:

We acknowledge the receipt on July 1, 1993 of your June 30 1993 supplemental new drug applications submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Zestril (lisinopril) Tablets (NDA 19-777) and Zestoretic (lisinopril/hydrochlorothiazide) Tablets (NDA 19-888).

We acknowledge receipt of your amendments dated August 3, 1993.

The supplemental applications are in response to our February 17, 1993 letters and provide for draft labeling revised to include a new subsection, **WARNINGS, Angioedema and Anaphylactoid Reactions** that includes three subsections, *Angioedema*, *Anaphylactoid Reactions Associated with Desensitization*, and *Anaphylactoid Reactions Associated with Hemodialysis*. The **PRECAUTIONS, Hemodialysis Patients** subsection has been deleted since the information is now under **WARNINGS**. In addition, the references throughout the labeling have been changed to reflect the above changes.

We have completed our review of these supplemental applications as submitted with draft labeling, as well as our reviews of labeling suggested by the other firms with approved NDAs for ACE inhibitors. We are asking you and the other firms to submit final printed labeling revised as follows (differences from our original request are underlined for your convenience):

WARNINGS

Anaphylactoid and Possibly Related Reactions

Presumably because angiotensin-converting enzyme inhibitors affect the metabolism of eicosanoids and polypeptides, including endogenous bradykinin, patients receiving ACE inhibitors (including [Trade name]) may be subject to a variety of adverse reactions, some of them serious.

Angioedema: (Same as current section).

Anaphylactoid reactions during desensitization: Two patients undergoing desensitizing treatment with hymenoptera venom while receiving ACE inhibitors sustained life-threatening anaphylactoid reactions. In the same patients, these reactions were avoided when ACE inhibitors were temporarily withheld, but they reappeared upon inadvertent rechallenge.

Anaphylactoid reactions during membrane exposure: Anaphylactoid reactions have been reported in patients dialyzed with high-flux membranes and treated concomitantly with an ACE inhibitor. Anaphylactoid reactions have also been reported in patients undergoing low-density lipoprotein apheresis with dextran sulfate absorption (a procedure dependent upon devices not approved in the United States).

PRECAUTIONS, Cough: Presumably due to the inhibition of the degradation of endogenous bradykinin, persistent nonproductive cough has been reported with all ACE inhibitors, always resolving after discontinuation of therapy. ACE inhibitor-induced cough should be considered in the differential diagnosis of cough.

In addition, please include cross references to these sections in appropriate places in your labeling.

If additional information relating to the safety or effectiveness of these drugs becomes available before we receive the final printed labeling, revision of that labeling may be required.

To each application, please submit twelve copies of the printed labeling seven of which are individually mounted on heavy weight paper or similar material.

Within 10 days after the date of this letter, you are required to amend the applications, notify us of your intent to file amendments, or follow one of your other options under 21 CFR 314.110. In the absence of such action FDA may take action to withdraw the supplemental applications.

Should you have any questions, please contact:

Ms. Kathleen Bongiovanni
Consumer Safety Officer
Telephone: (301) 443-4730

Sincerely yours,

9/24/93

Raymond J. Lipicky, M.D. 9-23-93
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-777/S-020
19-888/S-015

DEC 2 1994

Zeneca Pharmaceuticals Group
A business unit of Zeneca Inc.
Attention: William J. Kennedy, Ph.D.
P.O. Box 751
Wilmington, DE 19897

Dear Dr. Kennedy:

Please refer to your June 30, 1993 supplemental new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zestril (lisinopril) Tablets (NDA 19-777) and Zestoretic (lisinopril/hydrochlorothiazide) Tablets (NDA 19-888).

We acknowledge receipt of your amendments dated June 21, 1994.

The supplemental applications are in response to our February 17, 1993 letter and provide for draft labeling revised to include a new subsection, **WARNINGS, Angioedema and Anaphylactoid Reactions** that includes three subsection, *Angioedema*, *Anaphylactoid Reactions Associated with desensitization*, and *Anaphylactoid Reactions Associated with Hemodialysis*. The **PRECAUTIONS, Hemodialysis Patients** subsection has been deleted since the information is now under **WARNINGS.** In addition, the references throughout the labeling have been changed to reflect the above changes.

We have completed the review of these supplemental applications as submitted with draft labeling. Before these supplements may be approved, however, it will be necessary for you to submit final printed labeling (FPL). The labeling should be identical in content to the draft labeling included in the September 23, 1993 approvable letter for these supplements. In addition, for NDA 19-777, please replace the first word in the **DESCRIPTION** section, "Zestril," with "Lisinopril." Alternatively, the phrase, "a synthetic peptide derivative" could be deleted from the first sentence and added to the second sentence after the first word, "Lisinopril." In addition, all previous revisions as reflected in the most recently approved package inserts must be included. To facilitate review of your submissions, please provide highlighted or marked-up copies that show the changes that are being made.

If additional information relating to the safety or effectiveness of these drugs becomes available, revision of the FPL may be required.

Please submit fifteen copies of the printed labeling to each application ten of which are individually mounted on heavy weight paper or similar material.

Within 10 days after the date of this letter, you are required to amend these supplemental applications, 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 such action, FDA may take action to withdraw these supplemental applications.

Should you have any questions, please contact:

Ms. Kathleen Bongiovanni
Consumer Safety Officer
Telephone: (301) 594-5300

Sincerely yours,

12/2/94

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

Enclosure

cc:
Original NDA
HFC-130/JAllen
HFD-80
HFD-110
HFD-110/CSO
HFD-110/KBongiovanni;11/3/94
sb/11/3/94;11/25/94
R/D: JShort/11/4/94
RWolters/11/4/94
CResnick/11/5/94
SChen/11/7/94
NMorgenstern/11/22/94

K Bongiovanni 11-28-94

Approval Date: 19-777 - May 19, 1988
19-888 - July 20, 1989

APPROVABLE

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

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APR - 6 1995

NDA 19-777/S-020
19-888/S-015

Zeneca Pharmaceuticals
Attention: William J. Kennedy, Ph.D.
1800 Concord Pike
P.O. Box 15437
Wilmington, DE 19850-5437

Dear Dr. Kennedy:

Please refer to your June 30, 1993 supplemental new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zestril (lisinopril) Tablets (NDA 19-777) and Zestoretic (lisinopril/hydrochlorothiazide) Tablets (NDA 19-888).

We acknowledge receipt of your amendment dated February 23, 1995.

The supplemental applications provide for draft labeling revised as follows:

The first two sentences of the **DESCRIPTION** section have been revised as follows:

> Lisinopril is an oral long-acting angiotensin converting enzyme inhibitor. Lisinopril, a synthetic peptide derivative, is chemically . . ..

A new subsection, **WARNINGS, Angioedema and Anaphylactoid Reactions** that includes three subsections, *Angioedema, Anaphylactoid Reactions Associated with desensitization,* and *Anaphylactoid Reactions Associated with Hemodialysis* has been added. The **PRECAUTIONS, Hemodialysis Patients** subsection has been deleted since the information is now under **WARNINGS.** In addition, the references throughout the labeling have been changed to reflect the above changes.

We have completed the review of these supplemental applications as submitted with draft labeling. Before these supplements may be approved, however, it will be necessary for you to submit final printed labeling (FPL). The labeling should be identical in content to the February 23, 1995 draft with the following exception:

Please revise the first sentence of the **PRECAUTIONS, Cough** subsection to read:

> Presumably due to the inhibition of the degradation of endogenous bradykinin, persistent nonproductive cough has been reported with all ACE inhibitors, almost always resolving after discontinuation of therapy.

In addition, all previous revisions as reflected in the most recently approved package inserts must be included. To facilitate review of your submissions, please provide highlighted or marked-up copies that show the changes that are being made.

If additional information relating to the safety or effectiveness of these drugs becomes available, revision of the FPL may be required.

Please submit fifteen copies of the printed labeling to each application ten of which are individually mounted on heavy weight paper or similar material.

Within 10 days after the date of this letter, you are required to amend these supplemental applications, 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 such action, FDA may take action to withdraw these supplemental application.

These changes may not be implemented until you have been notified in writing that these supplemental applications are approved.

Should you have any questions, please contact:

Ms. Kathleen Bongiovanni
Consumer Safety Officer
Telephone: (301) 594-5300

Sincerely yours,

4/6/98

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