CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19777/S20

CORRESPONDENCE

ZENECA
Pharmaceuticals
A Business Unit of Zeneca Inc.

1800 Concord Pike
PO Box 15437
Wilmington, DE 19850-5437

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

MAY 18 1995

Dr. Raymond J. Lipicky
Division Director
Division of Cardio-Renal
Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
HFD No. 110, Room No. 16B-30
5600 Fishers Lane
Rockville, MD 20857

NDA SUPPL AMEND
AF
SLR-030

Dear Dr. Lipicky:

Re: ZESTORETIC® (lisinopril and hydrochlorothiazide) Tablets
NDA 19-888 (S-015 & S-020)
ZESTRIL® (lisinopril) Tablets
NDA 19-777 (S-020)

We take this opportunity to provide the Agency with final printed labeling for ZESTRIL® (lisinopril) and ZESTORETIC® (lisinopril and hydrochlorothiazide) Tablets as Rev B-1 04/95 (Tab 1). These labeling components have been revised to include a new section entitled WARNINGS, Anaphylactoid and Possibly Related Reactions, consisting of three subsections, Angioedema, Anaphylactoid Reactions During Desensitization, and Anaphylactoid Reactions During Membrane Exposure. The PRECAUTIONS - Cough subsection has also been revised.

The revisions to these labeling components are in response to the Agency's letters dated February 17, 1993, September 23, 1993 and November 9, 1994 (ZESTORETIC Only); December 2, 1994 and April 5, 1995 and Zeneca's supplemental applications dated June 30, 1993, June 21, 1994 and February 23, 1995.

For your convenience, enclosed as Tab 2 is a 3-column review document which clearly illustrates the changes being made herein. The left column represents current labeling; the middle column represents the labeling changes provided by the Agency in their above-referenced letters and agreed to previously by Zeneca; and the right column provides labeling changes agreed to between Zeneca and the Agency following Zeneca's supplemental application filed on February 23, 1995. The right column also provides supporting comments, when applicable.

ORIGINAL

Zeneca anticipates your approval of the enclosed final printed labeling. If you have any questions or need any additional information, please do not hesitate to contact me.

Sincerely,

Sandra L. Acquaviva
Assistant Manager, Marketed Products Group
Drug Regulatory Affairs Department
(302) 886-2192
(302) 886-2822 (fax)

SLA/SLR/mjb/3194/72&75

ZENECA
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1800 Concord Pike
PO Box 15437
Wilmington, DE 19850-5437

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

COPY 1

APR 11 1995

SUPPL NEW CORRESP
(NC)
S-020

Dr. Raymond J. Lipicky
Division Director
Division of Cardio-Renal
Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
HFD No. 110, Room No. 16B-30
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Lipicky:

Re: ZESTORETIC® (lisinopril and hydrochlorothiazide) Tablets
NDA 19-888 (S-015)
ZESTRIL® (lisinopril) Tablets
NDA 19-777 (S-020)

We take this opportunity to acknowledge receipt of your letter dated April 5, 1995 in response to our supplemental applications dated June 30, 1993; June 21, 1994; and February 23, 1995. These supplemental applications provided draft labeling revised to include a new section entitled WARNINGS, Anaphylactoid and Possibly Related Reactions with three subsections, Angioedema, Anaphylactoid Reactions During Desensitization, and Anaphylactoid Reactions During Membrane Exposure.

Zeneca Pharmaceuticals hereby notifies the FDA that it is our intent to file an amendment consisting of final printed labeling in the near future.

In the interim, if you have any questions or concerns, please do not hesitate to contact me.

Sincerely,

Sandra L. Acquaviva
Assistant Manager, Marketed Products Group
Drug Regulatory Affairs Department
(302) 886-2192
(302) 886-2822 (fax)

SLA/SLR/jr/3110/72/75

ORIGINAL

ZENECA
Pharmaceuticals
A Business Unit of Zeneca Inc.

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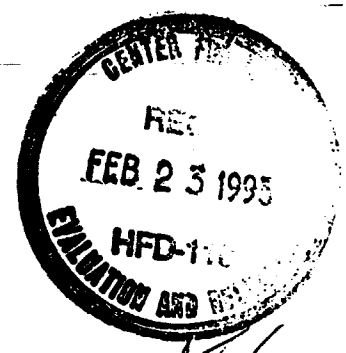

HAND DELIVERED

FEB 23 1995

2/27/95

NDA SUPPL AMEND (AL)
SLR-020

COPY 1

Dr. Raymond J. Lipicky
Division Director
Division of Cardio-Renal
Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
HFD No. 110, Room No. 16B-30
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Lipicky:

Re: ZESTRIL® (lisinopril) Tablets
NDA 19-777/S-020
ZESTORETIC® (lisinopril and hydrochlorothiazide) Tablets
NDA 19-888/S-015
Supplement - Expedited Review Requested

Reference is made to the Agency's letter dated December 2, 1994 in response to our June 30, 1993 and June 21, 1994 supplemental New Drug Applications submitted for ZESTRIL® (lisinopril) Tablets and ZESTORETIC® (lisinopril and hydrochlorothiazide) Tablets. These supplemental New Drug Applications provided draft labeling relative to anaphylactoid and possibly related reactions and proposed amendments to the Agency's final language relative to anaphylactoid and possibly related reactions, respectively.

Your December 2, 1994 letter requests final printed labeling identical to the labeling provided in your September 23, 1993 letter; however, Zeneca continues to strongly believe the following two proposed amendments to the Agency's class language more accurately reflect our experience with ZESTRIL and ZESTORETIC. In a telephone conversation on January 24, 1995 between the FDA and Zeneca, Zeneca agreed to provide alternative wording to the FDA in writing, hence this communication.

ORIGINAL

Zeneca believes the additional language in brackets below, which we added to the PRECAUTIONS section with our supplemental New Drug Application on March 4, 1993 for ZESTRIL (S-018) and ZESTORETIC (S-012), should be retained either in PRECAUTIONS or moved to the WARNINGS section along with the Agency's suggested language. We recently reviewed the 1995 Physicians' Desk Reference and found Capoten (captopril) and Monopril (fosinopril) have adopted the Agency's anaphylactoid and possibly related reactions class language and have retained the language in their PRECAUTIONS section similar to what we are proposing and seeking the Agency's concurrence in.

> **Anaphylactoid reactions during membrane exposure:** [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 type of dialysis membrane or 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).

Relative to the PRECAUTIONS-Cough subsection, we continue to believe it is appropriate to report that generally or almost always cough resolves after discontinuation of therapy. With the information available to us through spontaneous postmarketing reports and the enclosed article entitled "Nebulized Lidocaine in the Treatment of Refractory Cough" (Tab 1), we cannot state that cough always resolves following dechallenge. Our justification for this change from always to generally or almost always has been revised since our June 21, 1994 amendment and is enclosed as Tab 2.

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

For your convenience, enclosed as Tab 3 is draft labeling in the form of a 3-column review document. The left column represents current labeling; the middle column represents the Agency's language requested in the September 23, 1993 letter; and the right column represents our proposed modifications stated herein.

Zeneca requests an expedited review of the enclosed labeling. We would appreciate your rationale for not accepting these changes and/or approval of our proposed text at your earliest convenience so we may progress the class language to final printed labeling as requested.

If you have any questions or comments, please do not hesitate to contact me.

Sincerely,

Sandra L. Acquaviva
Assistant Manager, Marketed Products Group
Drug Regulatory Affairs Department
(302) 886-2192
(302) 886-2822 (fax)

SLA/SLR/jr/3015/72/75
Enclosures

Submitted in duplicate

ZENECA
Pharmaceuticals
A Business Unit of Zeneca Inc.

1800 Concord Pike
PO Box 15437
Wilmington, DE 19850-5437

SUPPLEMENT CORRECT?

DEC 12 1994

NC
S-020

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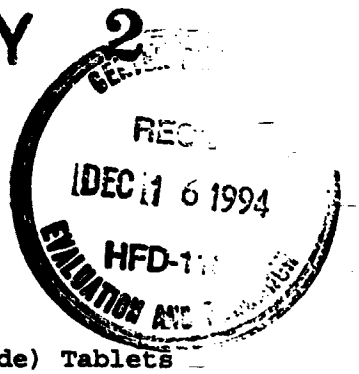
COPY 2



Dr. Raymond J. Lipicky
Division Director
Division of Cardio-Renal
Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
HFD No. 110, Room No. 16B-30
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Lipicky:

Re: ZESTORETIC® (lisinopril and hydrochlorothiazide) Tablets
NDA 19-888 (S-015)
ZESTRIL® (lisinopril) Tablets
NDA 19-777 (S-020)

We take this opportunity to acknowledge receipt of your letter dated December 2, 1994. This letter is in response to our supplemental applications dated June 30, 1993 and June 21, 1994 which provided draft labeling revised to include a new subsection entitled WARNINGS, Angioedema and Anaphylactoid Reactions, which includes three subsections, Angioedema, Anaphylactoid Reactions Associated with Hemodialysis, and Anaphylactoid Reactions Associated with Desensitization.

Zeneca Pharmaceuticals hereby notifies the FDA that it is our intent to file an amendment consisting of final printed labeling in the near future.

In the interim, if you have any questions or concerns, please do not hesitate to contact me.

Sincerely,

Sandra L. Acquaviva

Sandra L. Acquaviva
Assistant Manager, Marketed Products Group
Drug Regulatory Affairs Department
(302) 886-2192
(302) 886-2822 (fax)

SLA/SLR/jr/002831

ORIGINAL

ZENECA
Pharmaceuticals Group
ZENECA Pharmaceuticals, Stuart Pharmaceuticals
Business Units of ZENECA Inc.

COPY 1

1800 Concord Pike
Wilmington
Delaware 19897 USA

SUPPL NEW CORRESP
(N C)
S-020

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

OCT 11 1993

Dr. Raymond J. Lipicky
Division Director
Division of Cardio-Renal
Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
HFD No. 110, Room No. 16B-30
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Lipicky:

Re: ZESTORETIC® (lisinopril and hydrochlorothiazide) Tablets
NDA 19-888 (S-015)
ZESTRIL® (lisinopril) Tablets
NDA 19-777 (S-020)

We take this opportunity to acknowledge receipt of your letter dated September 23, 1993. This letter is in response to our supplemental applications which provided draft labeling to include new subsections in the WARNINGS section relative to Anaphylactoid Reactions.

Zeneca Pharmaceuticals Group hereby notifies the FDA that it is our intent to file an amendment consisting of final printed labeling in the near future.

In the interim, if you have any questions or concerns, please do not hesitate to contact me.

Sincerely,

Sandra L. Acquaviva
Assistant Manager, Marketed Products Group
Drug Regulatory Affairs Department
(302) 886-2192
(302) 886-2822 (fax)

SLA/SLR/jr

ORIGINAL

ZENECA
Pharmaceuticals Group
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1800 Concord Pike
Wilmington
Delaware 19897 USA

COPY

CERTIFIED MAIL
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NDA NO. 19-777 REF. NO. 5-020
NDA SUPPL FOR SLR
JUN 30 1993

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

Gentlemen:

Re: ZESTRIL® (lisinopril) Tablets
NDA 19-777
Draft Labeling

We take this opportunity to respond to the Agency's February 17, 1993 letter to Mr. George D. Alicknavitch regarding anaphylactoid reactions.

In response to your request, enclosed is draft labeling (Rev Q 04/93) in the form of a 3-column review document which clearly illustrates our proposed language for the WARNINGS section. The left column contains current labeling; the middle column represents our proposed language; and the right column is provided for comments, if applicable. The language you suggested has been modified slightly, with the exception of the subsection entitled "Anaphylactoid Reactions During Membrane Exposure." We chose to retain our language for this subsection as submitted with our March 4, 1993 letter; however, we have relocated this language from the PRECAUTIONS section to the WARNINGS section. We have done this because the procedure (ie, low density lipoprotein apheresis with dextran sulfate absorption) referenced in your language is not used or readily available in the United States. Our proposed labeling appears on pages 7, 8 and 9.

ORIGINAL

We understand we are not to revise our labeling until we receive a response to this letter. If you have any questions or concerns regarding this draft labeling, please do not hesitate to contact me.

Sincerely,

Sandra L. Acquaviva
Assistant Manager, Marketed Products Group
Drug Regulatory Affairs Department
(302) 886-2192
(302) 886-2822 (fax)

SLA/SLR/jr
Enclosure