CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19777/S20

ADMINISTRATIVE DOCUMENTS

DEC 2 1994

CSO Review of Labeling

NDA: 19-777/S-020 Zestril (lisinopril) Tablets
19-888/S-015 Zestoretic (lisinopril/HCTZ) Tablets

Date of submissions: June 21, 1994 (AL)

Date of receipt: June 21, 1994

Applicant: Zeneca Pharmaceuticals Group

Background: We issued supplement request letters on February 17, 1993, and asked all firms with approved ACE inhibitors to submit draft labeling revised to include information on "Anaphylactoid and Possibly Related Reactions" in the WARNINGS section, including subsections on angioedema, anaphylactoid reactions during desensitization, and anaphylactoid reactions during membrane exposure, and a revised PRECAUTIONS, Cough subsection. Zeneca responded with supplements dated June 30, 1993, received July 1, 1993. Additional information was received in amendments dated August 3, 1993, received August 9, 1993. We issued an approvable letter dated September 23, 1993, that asked for final printed labeling. Zeneca responded with revised draft labeling dated June 21, 1994.

Review: The proposed labeling differs from the requested text as follows:

Anaphylactoid reactions during desensitization: Zeneca proposed putting a footnote after the first sentence of this subsection, to refer the reader to the Lancet article from which the cases came. Drs. Lipicky and Fenichel disagreed with this proposal; it is our Division's policy to avoid the use of footnotes in labeling.

Anaphylactoid reactions during membrane exposure: Zeneca proposed adding information on the treatment of patients with this reaction. Dr. Lipicky disagreed with including this in the labeling. The firm also wished to specify one of the membrane types that has been associated with these reactions. Since we do not have data showing that any particular membrane is more or less likely than others to cause these reactions, this should not be included in the labeling.

Cough: Zeneca proposes adding the word "generally" instead of "always" in the sentence "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." Dr. Fenichel noted that any cases in which the cough did not resolve after discontinuation of therapy were due to other causes. He suggested leaving the sentence as it is, and Dr. Lipicky agreed.

In his review dated July 1, 1994, the chemist, Dr. Short, suggested that the first word of the DESCRIPTION section for NDA 19-777, "Zestril" be replaced with "Lisinopril." Dr. Wolters suggested the following alternative: the phrase "a synthetic peptide derivative" could be deleted from the first sentence and added to the second sentence after the first word, "Lisinopril." I will include a request for either of these changes to the approvable letter for NDA 19-777/S-020.

Recommendation: I will prepare an approvable letter for these supplements. These

supplements fall under 21 CFR 314.70 (c)(2)(i), Supplements for changes that may be made before FDA approval, to add or strengthen a contraindication, warning, precaution, or adverse reaction. I will request the revised wording for the DESCRIPTION section for Zestril.

/S/

Kathleen F. Bongiovanni 11-2-94

cc:

19-777/S-020
19-888/S-015
HFD-110 (both)
HFD-111/KBongiovanni
HFD-111/SBenton
kb/10/26/94.

CSO REVIEW OF LABELING

NDA 19-777/S-020 Zestril (lisinopril) Tablets

19-888/S-015 Zestoretic (lisinopril/hydrochlorothiazide) Tablets
/S-020

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

Dates of Submission: June 30, 1993 (19-777/S-020)
June 30, 1993 (19-888/S-015)
October 28, 1994 (19-888/S-020)

These supplemental applications were submitted and amended over a period of years and now provide for final printed labeling incorporating the following changes:

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 (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.)

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 "Therapy Guided by Clinical Effect" to "Dose Titration Guided by Clinical Effect."

Three approvable letters have been issued for supplemental applications 19-777/S-020 and 19-888/S-015 (September 23, 1993, December 2, 1994 and April 6, 1995). Upon review of the final printed labeling, all requested additions to the labeling have been incorporated. An approval letter will be drafted for Dr. Lipicky's signature.

/S/ 5/31/95

Gary Buehler

Orig NDAs
HFD-110 files
HFD-110 SBenton
HFD-110 KBongiovanni

CSO Review of Labeling

APR - 6 1995

NDA: 19-777/S-020 Zestril (lisinopril) Tablets
19-888/S-015 Zestoretic (lisinopril/HCTZ) Tablets

Date of submissions: February 23, 1995

Date of receipt: February 23, 1995

Applicant: Zeneca Pharmaceuticals Group

Background: We issued supplement request letters on February 17, 1993 asked all firms with approved ACE inhibitors to submit draft labeling revised to include information on "Anaphylactoid and Possibly Related Reactions" in the WARNINGS section, including subsections on angioedema, anaphylactoid reactions during desensitization, and anaphylactoid reactions during membrane exposure, and a revised PRECAUTIONS, Cough subsection. Zeneca responded with supplements dated June 30, 1993, received July 1, 1993. Additional information was received in amendments dated August 3, 1993, received August 9, 1993. We issued an approvable letter dated September 23, 1993, that asked for final printed labeling. Zeneca responded with revised draft labeling dated June 21, 1994. We responded with an approvable letter dated December 2, 1994, that asked for final printed labeling identical in content to the labeling included in the September 23, 1994 approvable letter, plus with a change recommended by the Chemist to the DESCRIPTION section. Zeneca has responded with another set of draft labeling.

Review: The proposed labeling differs from the requested text as follows:

NDA 19-777 & 19-888:

WARNINGS, Anaphylactoid reactions during membrane exposure: Zeneca proposes to add information to this subsection (additions underlined): 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 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).

PRECAUTIONS, Cough: Zeneca again proposes adding "generally" or "almost always" instead of "always" in the sentence "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." They had suggested this change in their June 21, 1994 submission. At that time Dr. Fenichel noted that any cases in which the cough did not resolve after discontinuation of therapy were due to other causes. He suggested leaving the sentence as it is, and Dr. Lipicky agreed. Dr. Chen did not object to the proposed changes. Upon review of the February 23, 1995 submission, Dr. Fenichel said "OK for anaphylactoid stuff; OK - but not a good idea - for "almost always;" "Generally or" not OK.

NDA 19-777:

DESCRIPTION: Based on Dr. Short's review dated July 1, 1994, the December 2, 1994 approvable letter asked the firm to replace the first word of 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 this submission, Zeneca has revised the first two sentences of the DESCRIPTION section as follows: "Lisinopril is an oral long-acting angiotensin converting enzyme inhibitor. Lisinopril, a synthetic peptide derivative, is chemically..."

Recommendation: I will prepare an approval letter for these supplements. These supplements fall under 21 CFR 314.70 (c)(2)(i), Supplements for changes that may be made before FDA approval, to add or strengthen a contraindication, warning, precaution, or adverse reaction.

/S/ 3-20-95

Kathleen F. Bongiovanni

cc:

19-777/S-020
19-888/S-015
HFD-110 (both)
HFD-111/KBongiovanni
HFD-111/SBenton

kb/3/17/95

CSO Review of Labeling

NDA	Drug	Date of Supplement	Date of Receipt	Date of Amendments
18-343/S-063	Capoten (captopril) Tablets	02-Apr-93	05-Apr-93	-
18-998/S-038	Vasotec (enalapril maleate) Tablets	26-May-93	01-Jun-93	-
19-221/S-017	Vaseretic (enalapril maleate/HCTZ) Tablets	26-May-93	01-~~Jun~~-93	-
19-309/S-015	Vasotec (enalaprilat) I.V.	26-May-93	01-Jun-93	-
19-558/S-022	Prinivil (lisinopril) Tablets	26-May-93	01-Jun-93	-
19-778/S-016	Prinzide (lisinopril/ HCTZ) Tablets	26-May-93	01-Jun-93	-
19-851/S-005	Lotensin (benazepril HCl) Tablets	17-Mar-93	22-Mar-93	-
20-033/S-003	Lotensin HCT (benazepril HCl/HCTZ) Tablets	17-Mar-93	22-Mar-93	-
19-885/S-003	Accupril (quinapril HCl) Tablets	09-Dec-92	11-Dec-92	31-Mar-93
19-901/SNC	Altace (ramipril) Capsules	17-Mar-93	23-Mar-93	-
19-777/S-020	Zestril (lisinopril) Tablets	30-Jun-93	01-Jul-93	03-Aug-93
19-888/S-015	Zestoretic (lisinopril/ HCTZ) Tablets	30-Jun-93	01-Jul-93	03-Aug-93

Background: We issued supplement request letters on February 17, 1993, that discussed proposed changes to the WARNINGS section of the labeling of all ACE inhibitors, including information from two recently published reports (in the Lancet) of anaphylactoid reactions in patients receiving ACE inhibitors during hymenoptera desensitization and during LDL apheresis. The letter asked the firms to submit draft labeling that includes language that combines the new information along with the angioedema, hemodialysis patients, and cough subsections of the labeling.

Review: When all of the firms except Zeneca (who usually follows Merck's lead on labeling) had submitted their proposed labeling, Dr. Fenichel reviewed them and developed uniform labeling . Dr. Lipicky reviewed Dr. Fenichel's suggestion (see attached, the column marked "FDA Revision") and recommended that we delete the first half of the first sentence of the WARNINGS, Anaphylactoid and Possibly Related Reactions subsection ("Presumably because angiotensin-converting enzyme is essential for degradation of endogenous bradykinin,"), but he said that if Dr. Fenichel thought it was important to the labeling, it could be kept. Dr. Fenichel did believe that it was important.

Zeneca subsequently submitted their draft labeling, and it included different information in the first sentence of the WARNINGS, Anaphylactoid and Possibly Related Reactions subsection:

"Presumably because angiotensin-converting enzyme inhibitors affect the metabolism of eicosanoids and polypeptides, including endogenous bradykinin." I called Mr. Anthony Rogers on July 21, 1993 and asked him to submit the basis for this labeling change. This amendment, dated August 3, 1993, arrived August 9, 1993.

Dr. Fenichel reviewed the amendment and decided that Zeneca's proposed language should be included in all labels (see Dr. Fenichel's note dated September 7, 1993 on the August 3, 1993 submission to 19-777).

Dr. Shaw Chen reviewed a Safety Report to NDA 19-558 dated August 16, 1993 (see his review dated August 26, 1993), on a patient who experienced a shock/hypotensive reaction while taking lisinopril and undergoing LDL apheresis. The patient had a positive re-challenge and de-challenge with lisinopril. Dr. Chen noted the existance of a similar report (WAES 93061328). Dr. Fenichel thought that once LDL apheresis is approved in the United States, we should include more information in the label on these adverse events. I asked Linda Dart at the Center for Devices and Radiologic Health, Office of Device Evaluation, Gastrointestinal and Renal Devices Branch about the status of these devices, and she said that they are still investigational and they do not expect them to be approved in the near future (see attached interoffice memo dated September 14, 1993).

Conclusion: I will prepare an approvable letter for the supplements and a supplement request letter for the application without a supplement, including our revised wording, asking for final printed labeling.

/S/

9-15-93

Kathleen F. Bongiovanni

cc:
18-343/S-063
18-998/S-038
19-221/S-017
19-309/S-015
19-558/S-022
19-778/S-016
19-851/S-005
20-033/S-003
19-885/S-003
19-901/SNC 3-17-93
19-777/S-020
19-888/S-015
HFD-110 (all)
HFD-111/SBenton
HFD-111/KBongiovanni