DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-777/S-018
19-888/S-012

MAR 31 1993

Zeneca Inc.
Attention: Mr. William A. Best
Route 202 at Murphy Road
Wilmington, DE 19897

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 Zestril (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

cc:
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 NMorgenstern

G Buehler 3/31/93

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

PROFESSIONAL INFORMATION BROCHURE

ZESTRIL®
LISINOPRIL-STUART

APPROVED

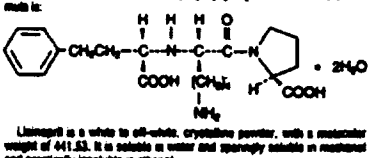
MAR 3 1 1993

USE IN PREGNANCY

When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, ZESTRIL should be discontinued as soon as possible. See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

DESCRIPTION

ZESTRIL® (lisinopril), a synthetic peptide derivative, is an oral long-acting angiotensin converting enzyme inhibitor. Lisinopril is chemically described as (S)-1-[N^{2}-(1-Carboxy-3-phenylpropyl)-L-lysyl]-L-proline dihydrate. Its empirical formula is $C_{21}H_{31}N_3O_5 \cdot 2H_2O$ and its structural formula is:



Lisinopril is a white to off-white, crystalline powder, with a molecular weight of 441.53. It is soluble in water and sparingly soluble in methanol and practically insoluble in ethanol.

ZESTRIL is supplied as 5 mg, 10 mg, 20 mg and 40 mg tablets for oral administration.

Inactive ingredients:

5, 10 and 20 mg tablets - calcium phosphate, magnesium stearate, mannitol, red ferric oxide, starch.

40 mg tablets - calcium phosphate, magnesium stearate, mannitol, starch, yellow ferric oxide.

CLINICAL PHARMACOLOGY

Mechanism of Action: Lisinopril inhibits angiotensin converting enzyme (ACE) in human subjects and animals. ACE is a peptidyl dipeptidase that catalyzes the conversion of angiotensin I to the vasoconstrictor substance, angiotensin II. Angiotensin II also stimulates aldosterone secretion by the adrenal cortex. Inhibition of ACE results in decreased plasma angiotensin II which leads to decreased vasopressor activity and to decreased aldosterone secretion. The latter decrease may result in a small increase of serum potassium. In hypertensive patients with normal renal function treated with ZESTRIL alone for up to 24 weeks, the mean increase in serum potassium was approximately 0.1 mEq/L; however, approximately 15% of patients had increases greater than 0.5 mEq/L and approximately 6% had a decrease greater than 0.5 mEq/L. In the same study, patients treated with ZESTRIL and hydrochlorothiazide for up to 24 weeks had a mean decrease in serum potassium of 0.1 mEq/L; approximately 4% of patients had increases greater than 0.5 mEq/L and approximately 12% had a decrease greater than 0.5 mEq/L. (See PRECAUTIONS.) Removal of angiotensin II negative feedback on renin secretion leads to increased plasma renin activity.

ACE is identical to kininase, an enzyme that degrades bradykinin. Whether increased levels of bradykinin, a potent vasodepressor peptide, play a role in the therapeutic effects of ZESTRIL remains to be elucidated.

While the mechanism through which ZESTRIL lowers blood pressure is believed to be primarily suppression of the renin-angiotensin-aldosterone system, ZESTRIL is antihypertensive even in patients with low-renin hypertension. Although ZESTRIL was antihypertensive in all races studied, black hypertensive patients (usually a low-renin hypertensive population) had a smaller average response to monotherapy than non-black patients.

Concomitant administration of ZESTRIL and hydrochlorothiazide further reduced blood pressure in black and non-black patients and any racial differences in blood pressure response were no longer evident.

Pharmacokinetics and Metabolism: Following oral administration of ZESTRIL, peak serum concentrations of lisinopril occur within about 7 hours. Declining serum concentrations exhibit a prolonged terminal phase which does not contribute to drug accumulation. This terminal phase probably represents saturable binding to ACE and is not proportional to dose. Lisinopril does not appear to be bound to other serum proteins.

Lisinopril does not undergo metabolism and is excreted unchanged entirely in the urine. Based on urinary recovery, the mean extent of absorption of lisinopril is approximately 25%, with large interindividual variability (6%-60%) at all doses tested (5-80 mg). Lisinopril absorption is not influenced by the presence of food in the gastrointestinal tract.

Upon multiple dosing, lisinopril exhibits an effective half-life of accumulation of 12 hours.

Impaired renal function decreases elimination of lisinopril, which is excreted principally through the kidneys, but this decrease becomes clinically important only when the glomerular filtration rate is below 30 mL/min. Above this glomerular filtration rate, the elimination half-life is little changed. With greater impairment, however, peak and trough lisinopril levels increase, time to peak concentration increases and time to attain steady state is prolonged. Older patients, on average, have approximately doubled higher blood levels and the area under the plasma concentration time curve (AUC) than younger patients. (See DOSAGE AND ADMINISTRATION.) Lisinopril can be removed by hemodialysis.

Studies in rats indicate that lisinopril crosses the blood-brain barrier poorly. Multiple doses of lisinopril in rats do not result in accumulation in any tissues. Milk of lactating rats contains radioactivity following administration of ^{14}C lisinopril. By whole body autoradiography, radioactivity was found in the placenta following administration of labeled drug to pregnant rats, but none was found in the fetuses.

Pharmacodynamics: Administration of ZESTRIL to patients with hypertension results in a reduction of both supine and standing blood pressure to about the same extent with no compensatory tachycardia. Symptomatic postural hypotension is usually not observed although it can occur and should be anticipated in volume and/or salt-depleted patients. (See WARNINGS.) When given together with thiazide-type diuretics, the blood pressure lowering effects of the two drugs are approximately additive.

In most patients studied, onset of antihypertensive activity was seen at one hour after oral administration of an individual dose of ZESTRIL, with peak reduction of blood pressure achieved by 6 hours. Although an antihypertensive effect was observed 24 hours after dosing with recommended single daily doses, the effect was more consistent and the mean effect was considerably larger in some studies with doses of 20 mg or more than with lower doses. However, at all doses studied, the 24 hour antihypertensive effect was substantially smaller 24 hours after dosing than it was 6 hours after dosing.

In some patients achievement of optimal blood pressure reduction may require two to four weeks of therapy.

The antihypertensive effects of ZESTRIL are maintained during long-term therapy. Abrupt withdrawal of ZESTRIL has not been associated with a rapid increase in blood pressure, or a significant increase in blood pressure compared to pretreatment levels.

Two dose-response studies utilizing a once daily regimen were conducted in 436 mild to moderate hypertensive patients not on a diuretic. Blood pressure was measured 24 hours after dosing. An antihypertensive effect of ZESTRIL was seen with 5 mg in some patients. However, in both studies blood pressure reductions occurred sooner and was greater in patients treated with 10, 20 or 80 mg of ZESTRIL. In controlled clinical studies, ZESTRIL 20-80 mg has been compared to patients with mild to moderate hypertension to hydrochlorothiazide 12.5-50 mg and with atenolol 50-200 mg, and in patients with moderate to severe hypertension to metoprolol 100-200 mg. It was superior to hydrochlorothiazide in effects on systolic and diastolic pressure in a population that was 344 Caucasian. ZESTRIL was approximately equivalent to atenolol and metoprolol in effects on diastolic blood pressure, and had somewhat greater effects on systolic blood pressure.

ZESTRIL had similar effectiveness and adverse effects in younger and older (> 65 years) patients. It was less effective in blacks than in Caucasians.

In hemodynamic studies in patients with essential hypertension, blood pressure reduction was accompanied by a reduction in peripheral arterial resistance with little or no change in cardiac output and in heart rate. In a study in nine hypertensive patients, following administration of ZESTRIL, there was an increase in mean renal blood flow that was not significant. Data from several small studies are inconsistent with respect to the effect of lisinopril on glomerular filtration rate in hypertensive patients with normal renal function, but suggest that changes, if any, are not large.

In patients with chronic stable hypertension ZESTRIL has been shown to be well tolerated and effective in controlling blood pressure. (See PRECAUTIONS.)

INDICATIONS AND USAGE

ZESTRIL is indicated for the treatment of hypertension. It may be used alone as initial therapy or concomitantly with other classes of antihypertensive agents.

In using ZESTRIL, consideration should be given to the fact that another angiotensin converting enzyme inhibitor, captopril, has caused agranulocytosis, particularly in patients with renal impairment or collagen vascular disease, and that available data are insufficient to show that ZESTRIL does not have a similar risk. (See WARNINGS.)

CONTRAINDICATIONS

ZESTRIL is contraindicated in patients who are hypersensitive to this product and in patients with a history of angioedema related to previous treatment with an angiotensin converting enzyme inhibitor.

WARNINGS

Angioedema: Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with angiotensin converting enzyme inhibitors, including ZESTRIL. In such cases, ZESTRIL should be promptly discontinued and appropriate therapy and monitoring should be provided until complete and sustained resolution of signs and symptoms has occurred. In instances where swelling has been confined to the face and lips the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms. Angioedema associated with laryngeal edema may be fatal. Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL) and/or measures necessary to ensure a patent airway should be promptly provided. (See ADVERSE REACTIONS.)

Hypotension: Excessive hypotension was rarely seen in uncomplicated hypertensive patients but is a possible consequence of the use with ZESTRIL in salt/volume-depleted persons, such as those treated vigorously with diuretics or patients on dialysis. (See PRECAUTIONS, Drug Interactions and ADVERSE REACTIONS.) In patients with severe congestive heart failure, with or without associated renal insufficiency, excessive hypotension has been observed and may be associated with oliguria and/or progressive azotemia, and rarely with acute renal failure and/or death. Because of the potential fall in blood pressure in these patients, therapy should be started under very close medical supervision. Such patients should be followed closely for the first two weeks of treatment and whenever the dose of ZESTRIL and/or diuretic is increased. Similar considerations apply to patients with ischemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

If hypotension occurs, the patient should be placed in supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further dose which usually can be given without difficulty once the blood pressure has increased after volume expansion.

Hepatic Failure: Antihypertensive therapy with ACE inhibitors may be associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up.

Neutropenia/Agranulocytosis: Another angiotensin converting enzyme inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients but more frequently in patients with renal impairment especially if they also have a collagen vascular disease. Available data from clinical trials of ZESTRIL are insufficient to show that ZESTRIL does not cause agranulocytosis at similar rates. Marketing experience has revealed rare cases of neutropenia and bone marrow depression in which a causal relationship to lisinopril cannot be excluded. Periodic monitoring of white blood cell counts in patients with collagen vascular disease and renal disease should be considered.

Fetal/Neonatal Morbidity and Mortality: ACE inhibitors can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature. When pregnancy is detected, ACE inhibitors should be discontinued as soon as possible.

The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to the ACE-inhibitor exposure.

These adverse effects do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to ACE inhibitors only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should make every effort to discontinue the use of ZESTRIL as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to ACE inhibitors will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intrauterine environment.

If oligohydramnios is observed, ZESTRIL should be discontinued unless it is considered lifesaving for the mother. Contraction stress testing (CST), a nonstress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of in utero exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function. Lisinopril, which crosses the placenta, has been removed from neonatal circulation by peritoneal dialysis with some clinical benefit, and theoretically may be removed by exchange transfusion, although there is no experience with the latter procedure.

No teratogenic effects of lisinopril were seen in studies of pregnant rats, mice, and rabbits. On a mg/kg basis, the doses used were up to 625 times (in mice), 188 times (in rats), and 6.6 times (in rabbits) the maximum recommended human dose.

PRECAUTIONS

General

Impaired Renal Function: As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe congestive heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin converting enzyme inhibitors, including ZESTRIL, may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death.

In hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine may occur. Experience with another angiotensin converting enzyme inhibitor suggests that these increases are usually reversible upon discontinuation of ZESTRIL and/or diuretic therapy. In such patients, renal function should be monitored during the first few weeks of therapy.

Some hypertensive patients with no apparent pre-existing renal vascular disease have developed increases in blood urea nitrogen and serum creatinine, usually minor and transient, especially when ZESTRIL has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction of ZESTRIL and/or discontinuation of the diuretic may be required.

Evaluation of the hypertensive patient should always include assessment of renal function. (See DOSAGE AND ADMINISTRATION.)

Hemodialysis Patients: 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 appropriate therapy for anaphylactoid reactions be instituted. 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.

Hyperkalemia: In clinical trials hyperkalemia (serum potassium greater than 5.7 mEq/L) occurred in approximately 2.2% of hypertensive patients and 4.9% of patients with congestive heart failure, in most cases these were isolated values which resolved despite continued therapy. Hyperkalemia was a cause of discontinuation of therapy in approximately 0.1% of hypertensive patients. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with ZESTRIL. (See Drug Interactions.)

Cough: Cough has been reported with the use of ACE inhibitors. Characteristically, the cough is nonproductive, persistent and resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough.

Surgery/Anesthesia: In patients undergoing major surgery or during anesthesia with agents that produce hypotension, ZESTRIL may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Information for Patients

Angioedema: Angioedema, including laryngeal edema, may occur especially following the first dose of ZESTRIL. Patients should be so advised and told to report immediately any signs or symptoms suggest-

(CONTINUED ON REVERSE SIDE)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19777/S18

CHEMISTRY REVIEW(S)

20.1
S-18
3-4-93

MAR 29 1993

CHEMIST'S REVIEW	1. ORGANIZATION HFD-110	2. NDA Number 19-777
3. Name and Address of Applicant (City & State) Zeneca Inc. Wilmington, DE 19897		4. Supplement(s) Number(s) S-018 Date(s) 4 Mar 93
5. Drug Name Zestril	6. Nonproprietary Name Lisinopril	7. Amendments & Other (reports, etc) - Dates
8. Supplement Provides For: Revised Package Insert (PI).		
9. Pharmacological Category Antihypertensive	10. How Dispensed ☐ Rx ☐ OTC	11. Related IND(s)/ NDA(s)/DMF(s) NDA 19-558 Prinivil, Merck
12. Dosage Form(s) TCM	13. Potency(ies) 2.5, 5, 10, 20, 40 mg	
14. Chemical Name and Structure		15. Records/Reports Current ☐ Yes ☐ No Reviewed ☐ Yes ☐ No

16. Comments:

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.

17. Conclusions and Recommendations:

APPROVABLE

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

18. REVIEWER /S/

Name James H.Short Date Completed 25 Mar 93

Distribution: ■ Original Jacket ☐ Reviewer ☐ Division File ☐ CSO

jhs/3/25/93/N19-777.S18 R/D Init: RWolters/3/25/93

3/29/93

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19777/S18

ADMINISTRATIVE DOCUMENTS

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:

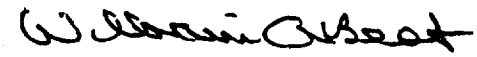
- Inclusion of "photosensitivity" to the listing of ADVERSE REACTIONS occurring in 0.3% to 1.0% of patients, SKIN-subsection. Please refer to page 18 of the enclosed 3-column document.

- 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,



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

WAB/SLR/rmw
Enclosures

MAR 31 1993

CSO REVIEW OF LABELING

NDA 19-777/S-018 Zestril (lisinopril) Tablets
NDA 19-888/S-012 Zestoretic (lisinopril with hydrochlorothiazide) Tablets

Zeneca Inc.
Wilmington, DE 19897

Date of Submissions: March 4, 1993

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/
/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

ZENECA

ZENECA Inc.
Wilmington
Delaware 19897

Telephone (302) 886-3000
Telex 4945649
Fax (302) 886-2972

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

NDA NO. 19-777 REF. NO. S-018

NDA SUPPL FOR SCR

MAR 04 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/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 continued 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.

ORIGINAL