Application Number: NDA 19777/S33

APPROVAL LETTER
Zeneica Pharmaceuticals
Attention: W.J. Kennedy, Ph.D.
1800 Concord Pike
P.O. Box 15437
Wilmington, DE 19850-5437

Dear Dr. Kennedy:

Please refer to your April 9, 1998 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zestril (lisinopril) 2.5, 5, 10, 20 and 40 mg Tablets.

The supplemental application provides for final printed labeling revised as follows:

**ADVERSE REACTIONS**, under "Other clinical adverse experiences occurring in 0.3% to 1% of patients with hypertension or heart failure treated with ZESTRIL in controlled clinical trials and rarer, serious, possibly drug-related events reported in uncontrolled studies or marketing experience are listed below, and within each category are in order of decreasing severity;" Respiratory System: "eosinophilic pneumonitis" has been added.

We have completed the review of this supplemental application and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the final printed labeling included with your submission dated April 9, 1998. Accordingly, the supplemental application is 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) 594-5334

Sincerely yours,

5/1/98

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/S33

FINAL PRINTED LABELING
ZESTRIL®
Lisinopril
PROFESSIONAL INFORMATION BROCHURE


DESCRIPTION
Lisinopril is a white or off-white, crystalline powder, with a molecular weight of 411.53. It is soluble in water and sparingly soluble in methanol and practically insoluble in ethanol.

CLINICAL PHARMACOLOGY
Mechanism of Action: Lisinopril inhibits angiotensin-converting enzyme (ACE) activity, converting angiotensin I to angiotensin II. ACE is a peptidyl dipeptidase that catalyzes the conversion of angiotensin I to angiotensin II. Inhibition of ACE also stimulates the conversion of angiotensin I to angiotensin II and increases circulating levels of angiotensin II, which results in increased sodium and water retention and increased aldosterone secretion by the adrenal cortex.

Pharmacokinetics: Lisinopril is rapidly absorbed after oral administration. Peak plasma concentrations are achieved within 1-4 hours. The drug is extensively metabolized in the liver to active metabolites, and the metabolites are excreted renally.

USE IN PREGNANCY
When used in pregnancy or in patients with severe hypertension, 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, Cardiovascular and Renal Effects.

CLINICAL STUDIES
Two randomized, double-blind studies were conducted to evaluate the efficacy and safety of ZESTRIL in patients with mild to moderate hypertension. In the first study, 247 patients were randomized to receive either ZESTRIL 2.5 mg/day or placebo. The mean decrease in sitting diastolic pressure was 5.5 mm Hg in the ZESTRIL group compared to 1.5 mm Hg in the placebo group. In the second study, 600 patients were randomized to receive either ZESTRIL 5 mg/day or placebo. The mean decrease in sitting diastolic pressure was 9.5 mm Hg in the ZESTRIL group compared to 3.0 mm Hg in the placebo group.

In a randomized, placebo-controlled trial in 103 patients with mild to moderate hypertension, ZESTRIL 2.5 mg/day produced a significant reduction in sitting diastolic pressure (mean change: -5.2 mm Hg vs. 0.7 mm Hg for placebo).

CONTRAINDICATIONS
ZESTRIL is contraindicated in patients with a history of angioedema with ACE inhibitors and patients who are hypersensitive to lisinopril or any other component of the formulation.

WARNINGS
Cardiovascular and Renal Effects
Hypotension: In patients with severe hypertension, ZESTRIL may cause a marked reduction in arterial pressure with initially small or no change in either cardiac output or heart rate. In a study in normotensive patients, following administration of ZESTRIL, there was an increase in mean blood pressure and heart rate. In patients with advanced heart failure, this effect may be more pronounced.

Renal Effects: When administered alone, ZESTRIL has been shown to cause a reduction in glomerular filtration rate and a reduction in renal blood flow and plasma renin activity.

Pregnancy: ZESTRIL should be discontinued as soon as possible in pregnant women.

PRECAUTIONS
Hypotension: ZESTRIL is contraindicated in patients with severe hypotension (systolic blood pressure <90 mm Hg).

ADVERSE REACTIONS
The most common adverse reactions associated with the use of ZESTRIL include cough, headache, nausea, diarrhea, constipation, and abdominal pain.

DRUG INTERACTIONS
ZESTRIL is not significantly affected by food or drug interactions.

DOSE AND ADMINISTRATION
The usual recommended dose is 5 mg/day, which may be increased to a maximum of 10 mg/day if needed.

OVERDOSAGE
In the event of an overdose, supportive and symptomatic treatment should be provided. Treatment should include monitoring of blood pressure, heart rate, and other vital signs. If necessary, supportive measures such as dialysis may be required.

REFERENCES
ACE-esterase suppressors that have been involved in the first trimester, hypotension in these suppressors may be caused by a decrease in blood pressure. During the first trimester, the blood pressure may be lower than normal due to an increase in sympathetic activity. This decrease in blood pressure may lead to a decrease in the perfusion of the placenta and the uterus, which can result in complications such as miscarriage and stillbirth.

In using ZESTRIL, concomitant use with other lipid-lowering agents, such as cholestyramine, may cause an increase in the risk of side effects. Therefore, ZESTRIL should be used with caution in patients with a history of these concomitant treatments, such as treatment with cholestyramine and/or bile acid sequestrant.

Warnings and Precautions

The use of ZESTRIL should be given attention to the fact that acute renal failure has been reported with ACE inhibitors. In pregnant women with pre-existing renal impairment, the use of ZESTRIL is not recommended. The risk of fetal wastage is not increased in pregnant women who have been on ZESTRIL for more than 4 weeks prior to delivery. If ZESTRIL is used in the second trimester of pregnancy, the risk of fetal malformation is not known. However, the use of ZESTRIL during the first trimester of pregnancy should be avoided.

In pregnant women, ZESTRIL should be used only if the benefit outweighs the potential risk to the fetus. If ZESTRIL is used during pregnancy, the patient should be informed of the possibility of fetal wastage and the need for follow-up care.
Bone Graft Adjustment in Patients With Hyperparathyroidism with Bone Impairment: In some patients treated with zoledronic acid, bone pain should be monitored closely. In patients with evidence of renal dysfunction, due to serum creatinine concentrations exceeding 3 mg/dL, the amount of dosage adjustments in Renal Failure patients with severe renal impairment has been performed. In general, in patients with bone pain, the amount of dosage adjustments was similar compared to patients with normal renal function.

Oral Suspension: 2.5 mg Tablets (Zoledronate SODINE 2.5 mg Tablets 1.5 mg/mL, Zoledronic acid, zoledronate 2.5 mg/mL) tablets is recommended for patients with severe renal impairment.

Zoledronic acid, zoledronate tablets (Zoledronate SODINE 2.5 mg Tablets 1.5 mg/mL, Zoledronic acid, zoledronate) tablets are not recommended in patients with severe renal impairment.

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RHPM Review of Labeling

NDA: 19-777/S-033 Zestril (lisinopril) Tablets

Date of submission: April 9, 1998

Date of receipt: April 10, 1998

Applicant: Zeneca Pharmaceuticals Group

Background: On September 19, 1997, we issued a supplement request letter, recommending that the ADVERSE REACTIONS section of the package inserts of ACE inhibitor products be revised to include eosinophilic pneumonitis.

Review: Zeneca has submitted a Special Supplement - Changes Being Effecte. The labeling changes will be implemented into production during the last week of April, 1998. The submitted final printed labeling has been revised as follows:

ADVERSE REACTIONS, Under “Other clinical adverse experiences occurring in 0.3% to 1% of patients with hypertension or heart failure treated with ZESTRIL in controlled clinical trials and rarer, serious, possibly drug-related events reported in uncontrolled studies or marketing experience are listed below, and within each category are in order of decreasing severity,” Respiratory System: “eosinophilic pneumonitis” has been added.

Recommendation: I will prepare an approval letter for this supplement for Dr. Lipicky's signature. It falls under 21 CFR 314.70 (c) Supplements for changes that may be made before FDA approval.

Kathleen F. Bongiovanni 4-21-98

cc: 19-777/S-033
    HFD-110
    HFD-110/KBongiovanni
    HFD-110/SBenton
    HF-2/MedWatch

kb/4/21/98.
Dr. Raymond J. Lipicky  
Division Director  
Division of Cardio-Renal  
Drug Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
ATTENTION: Document Control Room  
HFD No. 110  
1451 Rockville Pike  
Rockville, MD 20852

Dear Dr. Lipicky:

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

Reference is made to the Agency's September 19, 1997 letter which requested Zeneca revise the ADVERSE REACTION section of the ZESTRIL® (lisinopril) labeling to include eosinophilic pneumonitis. In accordance with your letter and CFR 314.70 (c), these labeling changes are reported as a Special Supplement - Changes Being Effected. These labeling changes are being implemented into production during the last week of April 1998.

For your convenience in reviewing, a three-column review document illustrating the labeling changes is provided in Tab 1. The left column represents the current ZESTRIL labeling, the middle column identifies the new text, and the right column provides comments. The revised text can be found on page 37 of Tab 1.

In addition, the sixteen copies of final printed labeling which were requested can be found in Tab 2. Ten of these labels are individually mounted, and six have been supplied in a clearly marked envelope in Tab 2.
If you have any questions or concerns, please do not hesitate to contact me.

Sincerely,

Robert J. Orzolek
Assistant Manager, Marketed Products Group
Drug Regulatory Affairs Department
(302) 886-4550
(302) 886-2822 (fax)

RJO/TGU/jr
Enclosures

Technical Review Copy: Ms. Kathleen F. Bongiovanni, HFD No. 110 (Cover Letter Only)