CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER(S)

NDA 19-777/S-037

Trade Name: Zestril 2.5, 5, 10, 20, 30, and 40 mg Tablets

Generic Name(s): (lisinopril)

Sponsor: Zeneca Pharmaceuticals

Agent:

Approval Date: February 7, 2000

Indication: Provides for changes in several sections of the package insert to incorporate statements concerning the use of high doses of lisinopril to reduce the risk of the combined outcomes of mortality and hospitalization in patients with congestive heart failure (based on ATLAS study)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

19-777/S-037

Approval Letter(s)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville MD 20857

NDA 19-777/S-037

FEB 7 2000

Zeneca Pharmaceuticals
Attention: Mr. Anthony F. Rogers
1800 Concord Pike
P.O. Box 15437
Wilmington, DE 19850-5437

Dear Mr. Rogers:

Please refer to your supplemental new drug application dated January 29, 1999, received February 2, 1999 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zestril (linsinopril) 2.5, 5, 10, 20, 30 and 40 mg Tablets.

We acknowledge receipt of your submissions dated December 13 and 30, 1999.

Your submission of December 30, 1999 constituted a complete response to our December 2, 1999 action letter.

This supplemental new drug application provides for changes in several sections of the package insert to incorporate statements concerning the use of high doses of lisinopril to reduce the risk of the combined outcomes of mortality and hospitalization in patients with congestive heart failure. These statements are based on the results of the "Assessment of Treatment with Lisinopril and Survival (ATLAS)" study.

We have completed the review of this supplemental new drug application, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the final printed labeling included in your December 30, 1999 submission. Accordingly, the supplemental new drug application is approved effective on the date of this letter.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

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 call:

Ms. Sandra L. Birdsong
Regulatory Project Manager
(301) 594-5312

Sincerely yours,

R Temple 2/7/00

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Archival NDA 19-777
HFD-110/Div. Files
HFD-110/S.Birdsong
HFD-110/Reviewers and Team Leaders
HF-2/MedWatch (with labeling)
HFD-002/ORM (with labeling)
HFD-101/ADRA (with labeling)
HFD-104/Peds/V.Kao (with labeling)
HFD-40/DDMAC (with labeling)
HFI-20/Press Office (with labeling)
HFD-400/OPDRA (with labeling)
HFD-613/OGD (with labeling)
HFD-21/ACS (with labeling) - ONLY for drug discussed at advisory committee meeting.
HFD-095/DDMS-IMT (with labeling)
HFD-810/DNDC Division Director
DISTRICT OFFICE

Drafted by: SB/January 18, 2000 asb 2/3/00
Initialed by:
In Draft: asb/1/18/00
final: asb/1/24/00
filename: 19-777AP.doc

P.M 1/28/2000

APPROVAL (AP)

4/28/00

2/2/2000

JH 1/27/00

RF 1/28/00

cc:
Archival NDA 19-777
HFD-110/Div. Files
HFD-110/S.Birdsong
HFD-110/Reviewers and Team Leaders
HF-2/MedWatch (with labeling)
HFD-002/ORM (with labeling)
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HFD-21/ACS (with labeling)
HFD-095/DDMS-IMT (with labeling)
HFD-810/DNDC Division Director
DISTRICT OFFICE
HFD-910/ MJ.HUNG

Drafted by: SB/January 18, 2000
Initialed by: N Morgenstern/2/1/00
In Draft: asb/1/18/00
Final: asb/1/24/00
Redrafted: 2/1/001
Final: asb/2/2/00
Filename: 19-777AP.doc

APPROVAL (AP)

AZ 2/2/00

JC 2/2/00

JW 2/2/00

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

19-777/S-037

Approvable Letter (S)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-777/S-037

DEC 2 - 1999

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

Dear Dr. Kennedy:

Please refer to your supplemental new drug application dated January 29, 1999, received February 2, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zestril (lisinopril) 2.5, 5, 10, 20, 30 and 40 mg Tablets.

We acknowledge receipt of your submissions dated July 15, September 3, October 1 and 19, and November 4 and 11, 1999.

This supplemental application proposes changes in several sections of the package insert to incorporate statements concerning the use of high doses of lisinopril to reduce the risk of the combined outcomes of mortality and hospitalization in patients with congestive heart failure. These statements are based on the results of the "Assessment of Treatment with Lisinopril and Survival (ATLAS)" study.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to submit final printed labeling (FPL) for the drug. The labeling should be identical in content to the enclosed marked-up draft labeling.

In addition, all previous revisions as reflected in the most recently approved labeling must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

You will note that not all of the changes you requested were found acceptable to us. At present, we do not think we can grant [ ], whether the claim is located in the Clinical Trials or the Indications and Usage section, on the basis of the results of ATLAS. We believe this is a close case, however, and would be pleased to discuss your presenting the ATLAS trial at a future Cardiovascular and Renal Drugs Advisory Committee meeting.

Please submit 20 copies of the final printed labeling, ten of which are individually mounted on heavy weight paper or similar material.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Cardio-Renal Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Within 10 days after the date of this letter, you are required to amend the supplemental application, 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 any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with these changes prior to approval of this supplemental application.
If you have any questions, please contact:

Ms. Sandra Birdsong
Regulatory Health Project Manager
(301) 594-5312.

Sincerely,

Robert Temple 12/2/99

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

cc:
Archival NDA 19-777
HFD-110/Div. Files
HFD-110/Z.McDonald
HFD-110/Reviewers and Team Leaders
HFD-002/ORM
HFD-101/ADRA
HFD-95/DDMS
HFD-40/DDMAC (with labeling)
DISTRICT OFFICE

11-15-99
K Srinivasan 11-15-99
Jim Burg 11-15-99
11/17/99
11-15-99
11/22/99

Drafted by: NAMorgenstern/August 6, 1999
Re-drafted by: ZMcDonald/November 10, 1999
Initialed by:
final: ASB
filename:

APPROVABLE (AE)

28 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

19-777/S-037

Approved Labeling

991206

F.P.O.

Rev U 12/99

PROFESSIONAL INFORMATION BROCHURE

ONCE-DAILY

ZESTRIL®

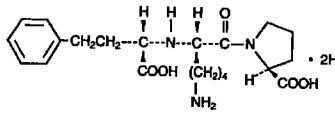
LISINOPRIL

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

Lisinopril is an oral long-acting angiotensin converting enzyme inhibitor. Lisinopril, a synthetic peptide derivative, 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 2.5 mg, 5 mg, 10 mg, 20 mg, 30 mg and 40 mg tablets for oral administration.

Inactive ingredients:

2.5 mg tablets - calcium phosphate, magnesium stearate, mannitol, starch.

5, 10, 20 and 30 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. The beneficial effects of lisinopril in hypertension and heart failure appear to result primarily from suppression of the renin-angiotensin-aldosterone system. 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 nonblack patients.

Concomitant administration of ZESTRIL and hydrochlorothiazide further reduced blood pressure in black and nonblack 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, although there was a trend to a small delay in time taken to reach peak serum concentrations in acute myocardial infarction patients. 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 intersubject variability (6%-60%) at all doses tested (5-80 mg). Lisinopril absorption is not influenced by the presence of food in the gastrointestinal tract. The absolute bioavailability of lisinopril is reduced to 16% in patients with stable NYHA Class II-III congestive heart failure, and the volume of distribution appears to be slightly smaller than that in normal subjects. The oral bioavailability of lisinopril in patients with acute myocardial infarction is similar to that in healthy volunteers.

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 and Clinical Effects

Hypertension: 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 mean 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 438 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 reduction 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 in 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 3/4 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 renovascular hypertension ZESTRIL has been shown to be well tolerated and effective in controlling blood pressure. (See PRECAUTIONS.)

Heart Failure: During baseline-controlled clinical trials, in patients receiving digitalis and diuretics, single doses of ZESTRIL resulted in decreases in pulmonary capillary wedge pressure, systemic vascular resistance and blood pressure accompanied by an increase in cardiac output and no change in heart rate.

In two placebo controlled, 12-week clinical studies using doses of ZESTRIL up to 20 mg, ZESTRIL as adjunctive therapy to digitalis and diuretics improved the following signs and symptoms due to congestive heart failure: edema, rales, paroxysmal nocturnal dyspnea and jugular venous distention. In one of the studies, beneficial response was also noted for: orthopnea, presence of third heart sound and the number of patients classified as NYHA Class III and IV. Exercise tolerance was also improved in this study. The once daily dosing for the treatment of congestive heart failure was the only dosage regimen used during clinical trial development and was determined by the measurement of hemodynamic response. A large (over 3000 patients) survival study, the ATLAS Trial, comparing 2.5 and 35 mg of lisinopril in patients with heart failure, showed that the higher dose of lisinopril had outcomes at least as favorable as the lower dose.

Acute Myocardial Infarction: The Gruppo Italiano per lo Studio della Sopravvienza nell'Infarto Miocardico (GISSI-3) study was a multicenter, controlled, randomized, unblinded clinical trial conducted in 19,394 patients with acute myocardial infarction admitted to a coronary care unit. It was designed to examine the effects of short-term (6 week) treatment with lisinopril, nitrates, their combination, or no therapy on short-term (6 week) mortality and on longer-term death and markedly impaired cardiac function. Patients presenting within 24 hours of the onset of symptoms who were hemodynamically stable were randomized, in a 2 x 2 factorial design, to six weeks of either 1) ZESTRIL alone (n=4841), 2) nitrates alone (n=4869), 3) ZESTRIL plus nitrates (n=4841), or 4) open control (n=4843). All patients received routine therapies, including thrombolytics (72%), aspirin (84%), and a beta-blocker (31%), as appropriate, normally utilized in acute myocardial infarction (MI) patients.

The protocol excluded patients with hypotension (systolic blood pressure ≤ 100 mmHg), severe heart failure, cardiogenic shock, and renal dysfunction (serum creatinine >2 mg/dL and/or proteinuria > 500 mg/24h). Doses of ZESTRIL were adjusted as necessary according to protocol (see DOSAGE AND ADMINISTRATION).

Study treatment was withdrawn at six weeks except where clinical conditions indicated continuation of treatment.

The primary outcomes of the trial were the overall mortality at 6 weeks and a combined endpoint at 6 months after the myocardial infarction, consisting of the number of patients who died, had late (day 4) clinical congestive heart failure, or had extensive left ventricular damage defined as ejection fraction ≤ 35% or an akinetic-dyskinetic [A-D] score ≥ 45%. Patients receiving ZESTRIL (n=9646), alone or with nitrates, had an 11% lower risk of death (2p [two-tailed] = 0.04) compared to patients receiving no ZESTRIL (n=9672) (6.4% vs. 7.2%, respectively) at six weeks. Although patients randomized to receive ZESTRIL for up to six weeks also fared numerically better on the combined end-point at 6 months, the open nature of the assessment of heart failure, substantial loss to follow-up echocardiography, and substantial excess use of lisinopril between 6 weeks and 6 months in the group randomized to 6 weeks of lisinopril, preclude any conclusion about this endpoint.

Patients with acute myocardial infarction, treated with ZESTRIL, had a higher (9.0% versus 3.7%) incidence of persistent hypotension (systolic blood pressure < 90 mmHg for more than 1 hour) and renal dysfunction (2.4% versus 1.1%) in-hospital and at six weeks (increasing creatinine concentration to over 3 mg/dL or a doubling or more of the baseline serum creatinine concentration). See ADVERSE REACTIONS - Acute Myocardial Infarction.

INDICATIONS AND USAGE

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

Heart Failure: ZESTRIL is indicated as adjunctive therapy in the management of heart failure in patients who are not responding adequately to diuretics and digitalis.

Acute Myocardial Infarction: ZESTRIL is indicated for the treatment of hemodynamically stable patients within 24 hours of acute myocardial infarction, to improve survival. Patients should receive, as appropriate, the standard recommended treatments such as thrombolytics, aspirin and beta-blockers.

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.)

In considering the use of ZESTRIL, it should be noted that in controlled trials ACE inhibitors have an effect on blood pressure that is less in black patients than in nonblacks. In addition, ACE inhibitors have been associated with a higher rate of angioedema in black than in nonblack patients (see WARNINGS, Angioedema).

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

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) may be subject to a variety of adverse reactions, some of them serious.

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. This may occur at any time during treatment. ACE inhibitors have been associated with a higher rate of angioedema in black than in nonblack patients. 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.)**

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor. (See also INDICATIONS AND USAGE and CONTRAINDICATIONS).

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: 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.

Hypotension: Excessive hypotension is rare in patients with uncomplicated hypertension treated with ZESTRIL alone.

Patients with heart failure given ZESTRIL commonly have some reduction in blood pressure, with peak blood pressure reduction occurring 6 to 8 hours post dose. Evidence from the two-dose ATLAS trial suggested that incidence of hypotension may increase with dose of lisinopril in heart failure patients. Discontinuation of therapy because of continuing symptomatic hypotension usually is not necessary when dosing instructions are followed; caution should be observed when initiating therapy. (See DOSAGE AND ADMINISTRATION.)

Patients at risk of excessive hypotension, sometimes associated with oliguria and/or progressive azotemia, and rarely with acute renal failure and/or death, include those with the following conditions or characteristics: heart failure with systolic blood pressure below 100 mmHg, hyponatremia, high dose diuretic therapy, recent intensive diuresis or increase in diuretic dose, renal dialysis, or severe volume and/or salt depletion of any etiology. It may be advisable to eliminate the diuretic (except in patients with heart failure), reduce the diuretic dose or increase salt intake cautiously before initiating therapy with ZESTRIL in patients at risk for excessive hypotension who are able to tolerate such adjustments. (See PRECAUTIONS, Drug Interactions and ADVERSE REACTIONS.)

Patients with acute myocardial infarction in the GISSI-3 trial had a higher (9.0% versus 3.7%) incidence of persistent hypotension (systolic blood pressure < 90 mmHg for more than 1 hour) when treated with ZESTRIL. Treatment with ZESTRIL must not be initiated in acute myocardial infarction patients at risk of further serious hemodynamic deterioration after treatment with a vasodilator (e.g., systolic blood pressure of 100 mmHg or lower) or cardiogenic shock.

In patients at risk of excessive hypotension, therapy should be started under very close medical supervision and 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 may apply to patients with ischemic heart or cerebrovascular disease, or in patients with acute myocardial infarction, in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

If excessive hypotension occurs, the patient should be placed in the supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses of ZESTRIL which usually can be given without difficulty once the blood pressure has stabilized. If symptomatic hypotension develops, a dose reduction or discontinuation of ZESTRIL or concomitant diuretic may be necessary.

Leukopenia/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 leukopenia/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.

Hepatic Failure: Rarely, ACE inhibitors have been 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.

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 intraamniotic 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 0.6 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 patients with hypertension or heart failure 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 and/or discontinuation of the diuretic and/or ZESTRIL may be required.

Patients with acute myocardial infarction in the GISSI-3 trial, treated with ZESTRIL had a higher (2.4% versus 1.1%) incidence of renal dysfunction in-hospital and at six weeks (increasing creatinine concentration to over 3 mg/dL or a doubling or more of the baseline serum creatinine concentration). In acute myocardial infarction, treatment with ZESTRIL should be initiated with caution in patients with evidence of renal dysfunction, defined as serum creatinine concentration exceeding 2 mg/dL. If renal dysfunction develops during treatment with ZESTRIL (serum creatinine concentration exceeding 3 mg/dL or a doubling from the pre-treatment value) then the physician should consider withdrawal of ZESTRIL.

Evaluation of patients with hypertension, heart failure, or myocardial infarction should always include assessment of renal function. (See DOSAGE AND ADMINISTRATION.)

Hyperkalemia: In clinical trials hyperkalemia (serum potassium greater than 5.7 mEq/L) occurred in approximately 2.2% of hypertensive patients and 4.8% of patients with 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; 0.6% of patients with heart failure and 0.1% of patients with myocardial infarction. 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: 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.

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 at any time during treatment with angiotensin converting enzyme inhibitors, including ZESTRIL. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to take no more drug until they have consulted with the prescribing physician.

Symptomatic Hypotension: Patients should be cautioned to report lightheadedness especially during the first few days of therapy. If actual syncope occurs, the patient should be told to discontinue the drug until they have consulted with the prescribing physician.

All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure; patients should be advised to consult with their physician.

Hyperkalemia: Patients should be told not to use salt substitutes containing potassium without consulting their physician.

Leukopenia/Neutropenia: Patients should be told to report promptly any indication of infection (e.g., sore throat, fever) which may be a sign of leukopenia/neutropenia.

Pregnancy: Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to ACE inhibitors, and they should also be told that these consequences do not

(CONTINUED ON REVERSE SIDE)

appear to have resulted from intrauterine ACE inhibitor exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

NOTE: As with many other drugs, certain advice to patients being treated with ZESTRIL is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Drug Interactions

Hypotension - Patients on Diuretic Therapy: Patients on diuretics and especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with ZESTRIL. The possibility of hypotensive effects with ZESTRIL can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with ZESTRIL. If it is necessary to continue the diuretic, initiate therapy with ZESTRIL at a dose of 5 mg daily, and provide close medical supervision after the initial dose until blood pressure has stabilized. (See WARNINGS, and DOSAGE AND ADMINISTRATION.) When a diuretic is added to the therapy of a patient receiving ZESTRIL, an additional antihypertensive effect is usually observed. Studies with ACE inhibitors in combination with diuretics indicate that the dose of the ACE inhibitor can be reduced when it is given with a diuretic. (See DOSAGE AND ADMINISTRATION.)

Indomethacin: In a study in 36 patients with mild to moderate hypertension where the antihypertensive effects of ZESTRIL alone were compared to ZESTRIL given concomitantly with indomethacin, the use of indomethacin was associated with a reduced effect, although the difference between the two regimens was not significant.

Other Agents: ZESTRIL has been used concomitantly with nitrates and/or digoxin without evidence of clinically significant adverse interactions. This included post myocardial infarction patients who were receiving intravenous or transdermal nitroglycerin. No clinically important pharmacokinetic interactions occurred when ZESTRIL was used concomitantly with propranolol or hydrochlorothiazide. The presence of food in the stomach does not alter the bioavailability of ZESTRIL.

Agents Increasing Serum Potassium: ZESTRIL attenuates potassium loss caused by thiazide-type diuretics. Use of ZESTRIL with potassium-sparing diuretics (e.g., spironolactone, triamterene or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Therefore, if concomitant use of these agents is indicated because of demonstrated hypokalemia, they should be used with caution and with frequent monitoring of serum potassium. Potassium sparing agents should generally not be used in patients with heart failure who are receiving ZESTRIL.

Lithium: Lithium toxicity has been reported in patients receiving lithium concomitantly with drugs which cause elimination of sodium, including ACE inhibitors. Lithium toxicity was usually reversible upon discontinuation of lithium and the ACE inhibitor. It is recommended that serum lithium levels be monitored frequently if ZESTRIL is administered concomitantly with lithium.

Carcinogenesis, Mutagenesis, Impairment of Fertility: There was no evidence of a tumorigenic effect when lisinopril was administered for 105 weeks to male and female rats at doses up to 90 mg/kg/day (about 56 or 9 times* the maximum recommended daily human dose, based on body weight and body surface area, respectively). There was no evidence of carcinogenicity when lisinopril was administered for 92 weeks to (male and female) mice at doses up to 135 mg/kg/day (about 84 times* the maximum recommended daily human dose). This dose was 6.8 times the maximum human dose based on body surface area in mice.

*Calculations assume a human weight of 50 kg and human body surface area of 1.62 m^2.

Lisinopril was not mutagenic in the Ames microbial mutagen test with or without metabolic activation. It was also negative in a forward mutation assay using Chinese hamster lung cells. Lisinopril did not produce single strand DNA breaks in an *in vitro* alkaline elution rat hepatocyte assay. In addition, lisinopril did not produce increases in chromosomal aberrations in an *in vitro* test in Chinese hamster ovary cells or in an *in vivo* study in mouse bone marrow.

There were no adverse effects on reproductive performance in male and female rats treated with up to 300 mg/kg/day of lisinopril. This dose is 188 times and 30 times the maximum human dose when based on mg/kg and mg/m^2, respectively.

Pregnancy

Pregnancy Categories C (first trimester) and D (second and third trimesters). See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

Nursing Mothers: Milk of lactating rats contains radioactivity following administration of ^{14}C lisinopril. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from ACE inhibitors, a decision should be made whether to discontinue nursing and/or discontinue ZESTRIL, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

ZESTRIL has been found to be generally well tolerated in controlled clinical trials involving 1969 patients with hypertension or heart failure. For the most part, adverse experiences were mild and transient.

Hypertension:

In clinical trials in patients with hypertension treated with ZESTRIL, discontinuation of therapy due to clinical adverse experiences occurred in 5.7% of patients. The overall frequency of adverse experiences could not be related to total daily dosage within the recommended therapeutic dosage range.

For adverse experiences occurring in greater than 1% of patients with hypertension treated with ZESTRIL or ZESTRIL plus hydrochlorothiazide in controlled clinical trials, and more frequently with ZESTRIL and/or ZESTRIL plus hydrochlorothiazide than placebo, comparative incidence data are listed in the table below:

PERCENT OF PATIENTS IN CONTROLLED STUDIES

	ZESTRIL (n=1349) Incidence (discontinuation)	ZESTRIL/ Hydrochlorothiazide (n=529) Incidence (discontinuation)	PLACEBO (n=207) Incidence (discontinuation)
Body as a Whole			
Fatigue	2.5 (0.3)	4.0 (0.5)	1.0 (0.0)
Asthenia	1.3 (0.5)	2.1 (0.2)	1.0 (0.0)
Orthostatic Effects	1.2 (0.0)	3.5 (0.2)	1.0 (0.0)
Cardiovascular			
Hypotension	1.2 (0.5)	1.6 (0.5)	0.5 (0.5)
Digestive			
Diarrhea	2.7 (0.2)	2.7 (0.3)	2.4 (0.0)
Nausea	2.0 (0.4)	2.5 (0.2)	2.4 (0.0)
Vomiting	1.1 (0.2)	1.4 (0.1)	0.5 (0.0)
Dyspepsia	0.9 (0.0)	1.9 (0.0)	0.0 (0.0)
Musculoskeletal			
Muscle Cramps	0.5 (0.0)	2.9 (0.8)	0.5 (0.0)
Nervous/Psychiatric			
Headache	5.7 (0.2)	4.5 (0.5)	1.9 (0.0)
Dizziness	5.4 (0.4)	9.2 (1.0)	1.9 (0.0)
Paresthesia	0.8 (0.1)	2.1 (0.2)	0.0 (0.0)
Decreased Libido	0.4 (0.1)	1.3 (0.1)	0.0 (0.0)
Vertigo	0.2 (0.1)	1.1 (0.2)	0.0 (0.0)
Respiratory			
Cough	3.5 (0.7)	4.6 (0.8)	1.0 (0.0)
Upper Respiratory Infection	2.1 (0.1)	2.7 (0.1)	0.0 (0.0)
Common Cold	1.1 (0.1)	1.3 (0.1)	0.0 (0.0)
Nasal Congestion	0.4 (0.1)	1.3 (0.1)	0.0 (0.0)
Influenza	0.3 (0.1)	1.1 (0.1)	0.0 (0.0)
Skin			
Rash	1.3 (0.4)	1.6 (0.2)	0.5 (0.5)
Urogenital			
Impotence	1.0 (0.4)	1.6 (0.5)	0.0 (0.0)

Chest pain and back pain were also seen, but were more common on placebo than ZESTRIL.

Heart Failure:

In patients with heart failure treated with ZESTRIL for up to four years, discontinuation of therapy due to clinical adverse experiences occurred in 11.0% of patients. In controlled studies in patients with heart failure, therapy was discontinued in 8.1% of patients treated with ZESTRIL for 12 weeks, compared to 7.7% of patients treated with placebo for 12 weeks.

The following table lists those adverse experiences which occurred in greater than 1% of patients with heart failure treated with ZESTRIL or placebo for up to 12 weeks in controlled clinical trials, and more frequently on ZESTRIL than placebo.

	Controlled Trials	
	ZESTRIL (n=407) Incidence (discontinuation) 12 weeks	Placebo (n=155) Incidence (discontinuation) 12 weeks
Body as a Whole		
Chest Pain	3.4 (0.2)	1.3 (0.0)
Abdominal Pain	2.2 (0.7)	1.9 (0.0)
Cardiovascular		
Hypotension	4.4 (1.7)	0.6 (0.6)
Digestive		
Diarrhea	3.7 (0.5)	1.9 (0.0)
Nervous/Psychiatric		
Dizziness	11.8 (1.2)	4.5 (1.3)
Headache	4.4 (0.2)	3.9 (0.0)
Respiratory		
Upper Respiratory Infection	1.5 (0.0)	1.3 (0.0)
Skin		
Rash	1.7 (0.5)	0.6 (0.6)

Also observed at > 1% with ZESTRIL but more frequent or as frequent on placebo than ZESTRIL in controlled trials were asthenia, angina pectoris, nausea, dyspnea, cough, and pruritus.

Worsening of heart failure, anorexia, increased salivation, muscle cramps, back pain, myalgia, depression, chest sound abnormalities, and pulmonary edema were also seen in controlled clinical trials, but were more common on placebo than ZESTRIL.

In the two-dose ATLAS trial in heart failure patients, withdrawals due to adverse events were not different between the low and high groups, either in total number of discontinuation (17-18%) or in rare specific events (<1%). The following adverse events, mostly related to ACE inhibition, were reported more commonly in the high dose group:

% of patients Events	High Dose (N=1568)	Low Dose (N=1596)
Dizziness	18.9	12.1
Hypotension	10.8	6.7
Creatinine increased	9.9	7.0
Hyperkalemia	6.4	3.5
NPN* increased	9.2	6.5
Syncope	7.0	5.1

*NPN = non-protein nitrogen

Acute Myocardial Infarction: In the GISSI-3 trial, in patients treated with ZESTRIL for six weeks following acute myocardial infarction, discontinuation of therapy occurred in 17.6% of patients.

Patients treated with ZESTRIL had a significantly higher incidence of hypotension and renal dysfunction compared with patients not taking ZESTRIL.

In the GISSI-3 trial, hypotension (9.7%), renal dysfunction (2.0%), cough (0.5%), post infarction angina (0.3%), skin rash and generalized edema (0.01%), and angioedema (0.01%) resulted in withdrawal of treatment. In elderly patients treated with ZESTRIL, discontinuation due to renal dysfunction was 4.2%.

Other clinical adverse experiences occurring in 0.3% to 1.0% 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:

Body as a Whole: Anaphylactoid reactions (see WARNINGS, Anaphylactoid Reactions During Membrane Exposure), syncope, orthostatic effects, chest discomfort, pain, pelvic pain, flank pain, edema, facial edema, virus infection, fever, chills, malaise.

Cardiovascular: Cardiac arrest; myocardial infarction or cerebrovascular accident possibly secondary to excessive hypotension in high risk patients (see WARNINGS, Hypotension); pulmonary embolism and infarction, arrhythmias (including ventricular tachycardia, atrial tachycardia, atrial fibrillation, bradycardia and premature ventricular contractions), palpitations, transient ischemic attacks, paroxysmal nocturnal dyspnea, orthostatic hypotension, decreased blood pressure, peripheral edema, vasculitis.

Digestive: Pancreatitis, hepatitis (hepatocellular or cholestatic jaundice) (see WARNINGS, Hepatic Failure), vomiting, gastritis, dyspepsia, heartburn, gastrointestinal cramps, constipation, flatulence, dry mouth.

Hematologic: Rare cases of bone marrow depression, hemolytic anemia, leukopenia/neutropenia and thrombocytopenia.

Endocrine: Diabetes mellitus.

Metabolic: Weight loss, dehydration, fluid overload, gout, weight gain.

Musculoskeletal: Arthritis, arthralgia, neck pain, hip pain, low back pain, joint pain, leg pain, knee pain, shoulder pain, arm pain, lumbago.

Nervous System/Psychiatric: Stroke, ataxia, memory impairment, tremor, peripheral neuropathy (e.g., dysesthesia), spasm, paresthesia, confusion, insomnia, somnolence, hypersomnia, irritability and nervousness.

Respiratory System: Malignant lung neoplasms, hemoptysis, pulmonary infiltrates, bronchospasm, asthma, pleural effusion, pneumonia, eosinophilic pneumonitis, bronchitis, wheezing, orthopnea, painful respiration, epistaxis, laryngitis, sinusitis, pharyngeal pain, pharyngitis, rhinitis, rhinorrhea.

Skin: Urticaria, alopecia, herpes zoster, photosensitivity, skin lesions, skin infections, pemphigus, erythema, flushing, diaphoresis. Other severe skin reactions have been reported rarely, including toxic epidermal necrolysis and Stevens-Johnson syndrome; causal relationship has not been established.

Special Senses: Visual loss, diplopia, blurred vision, tinnitus, photophobia, taste alteration.

Urogenital System: Acute renal failure, oliguria, anuria, uremia, progressive azotemia, renal dysfunction, (see PRECAUTIONS and DOSAGE AND ADMINISTRATION), pyelonephritis, dysuria, urinary tract infection, breast pain.

Miscellaneous: A symptom complex has been reported which may include a positive ANA, an elevated erythrocyte sedimentation rate, arthralgia/arthritis, myalgia, fever, vasculitis, eosinophilia and leukocytosis. Rash, photosensitivity or other dermatological manifestations may occur alone or in combination with these symptoms.

ANGIOEDEMA: Angioedema has been reported in patients receiving ZESTRIL (0.1%). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis and/or larynx occurs, treatment with ZESTRIL should be discontinued and appropriate therapy instituted immediately. (See WARNINGS.)

HYPOTENSION: In hypertensive patients, hypotension occurred in 1.2% and syncope occurred in 0.1% of patients. Hypotension or syncope was a cause of discontinuation of therapy in 0.5% of hypertensive patients. In patients with heart failure, hypotension occurred in 5.3% and syncope occurred in 1.8% of patients. These adverse experiences were possibly dose-related (see above data from ATLAS Trial) and caused discontinuation of therapy in 1.8% of these patients in the symptomatic trials. In patients treated with ZESTRIL for six weeks after acute myocardial infarction, hypotension (systolic blood pressure ≤100 mmHg) resulted in discontinuation of therapy in 9.7% of the patients. (See WARNINGS.)

Fetal/Neonatal Morbidity and Mortality: See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

Cough: See PRECAUTIONS - Cough

Clinical Laboratory Test Findings

Serum Electrolytes: Hyperkalemia (See PRECAUTIONS), hyponatremia.

Creatinine, Blood Urea Nitrogen: Minor increases in blood urea nitrogen and serum creatinine, reversible upon discontinuation of therapy, were observed in about 2.0% of patients with essential hypertension treated with ZESTRIL alone. Increases were more common in patients receiving concomitant diuretics and in patients with renal artery stenosis. (See PRECAUTIONS.) Reversible minor increases in blood urea nitrogen and serum creatinine were observed in approximately 11.6% of patients with heart failure on concomitant diuretic therapy. Frequently, these abnormalities resolved when the dosage of the diuretic was decreased.

Hemoglobin and Hematocrit: Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.4 g% and 1.3 vol%, respectively) occurred frequently in patients treated with ZESTRIL but were rarely of clinical importance in patients without some other cause of anemia. In clinical trials, less than 0.1% of patients discontinued therapy due to anemia.

Liver Function Tests: Rarely, elevations of liver enzymes and/or serum bilirubin have occurred. (See WARNINGS, Hepatic Failure.)

In hypertensive patients, 2.0% discontinued therapy due to laboratory adverse experiences, principally elevations in blood urea nitrogen (0.6%), serum creatinine (0.5%) and serum potassium (0.4%).

In the heart failure trials, 3.4% of patients discontinued therapy due to laboratory adverse experiences; 1.8% due to elevations in blood urea nitrogen and/or creatinine and 0.6% due to elevations in serum potassium.

In the myocardial infarction trial, 2.0% of patients receiving ZESTRIL discontinued therapy due to renal dysfunction (increasing creatinine concentration to over 3 mg/dL or a doubling or more of the baseline serum creatinine concentration); less than 1.0% of patients discontinued therapy due to other laboratory adverse experiences: 0.1% with hyperkalemia and less than 0.1% with hepatic enzyme alterations.

OVERDOSAGE

Following a single oral dose of 20 g/kg no lethality occurred in rats, and death occurred in one of 20 mice receiving the same dose. The most likely manifestation of overdosage would be hypotension, for which the usual treatment would be intravenous infusion of normal saline solution.

Lisinopril can be removed by hemodialysis.

DOSAGE AND ADMINISTRATION

Hypertension

Initial Therapy: In patients with uncomplicated essential hypertension not on diuretic therapy, the recommended initial dose is 10 mg once a day. Dosage should be adjusted according to blood pressure response. The usual dosage range is 20 to 40 mg per day administered in a single daily dose. The antihypertensive effect may diminish toward the end of the dosing interval regardless of the administered dose, but most commonly with a dose of 10 mg daily. This can be evaluated by measuring blood pressure just prior to dosing to determine whether satisfactory control is being maintained for 24 hours. If it is not, an increase in dose should be considered. Doses up to 80 mg have been used but do not appear to give greater effect. If blood pressure is not controlled with ZESTRIL alone, a low dose of a diuretic may be added. Hydrochlorothiazide, 12.5 mg has been shown to provide an additive effect. After the addition of a diuretic, it may be possible to reduce the dose of ZESTRIL.

Diuretic Treated Patients: In hypertensive patients who are currently being treated with a diuretic, symptomatic hypotension may occur occasionally following the initial dose of ZESTRIL. The diuretic should be discontinued, if possible, for two to three days before beginning therapy with ZESTRIL to reduce the likelihood of hypotension. (See WARNINGS.) The dosage of ZESTRIL should be adjusted according to blood pressure response. If the patient's blood pressure is not controlled with ZESTRIL alone, diuretic therapy may be resumed as described above.

If the diuretic cannot be discontinued, an initial dose of 5 mg should be used under medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and PRECAUTIONS, Drug Interactions.)

Concomitant administration of ZESTRIL with potassium supplements, potassium salt substitutes, or potassium-sparing diuretics may lead to increases of serum potassium. (See PRECAUTIONS.)

Dosage Adjustment in Renal Impairment: The usual dose of ZESTRIL (10 mg) is recommended for patients with creatinine clearance > 30 mL/min (serum creatinine of up to approximately 3 mg/dL). For patients with creatinine clearance ≥ 10 mL/min ≤ 30 mL/min (serum creatinine ≥ 3 mg/dL), the first dose is 5 mg once daily. For patients with creatinine clearance < 10 mL/min (usually on hemodialysis) the recommended initial dose is 2.5 mg. The dosage may be titrated upward until blood pressure is controlled or to a maximum of 40 mg daily.

Renal Status	Creatinine Clearance mL/min	Initial Dose mg/day
Normal Renal Function to Mild Impairment	> 30	10
Moderate to Severe Impairment	≥ 10 ≤ 30	5
Dialysis Patients*	< 10	2.5**

* See WARNINGS, Anaphylactoid Reactions During Membrane Exposure.

** Dosage interval should be adjusted depending on the blood pressure response.

Heart Failure

ZESTRIL is indicated as adjunctive therapy with diuretics and (usually) digitalis. The recommended starting dose is 5 mg once a day. When initiating treatment with lisinopril in patients with heart failure, the initial dose should be administered under medical observation, especially in those patients with low blood pressure (systolic blood pressure below 100 mmHg). The mean peak blood pressure lowering occurs six to eight hours after dosing. Observation should continue until blood pressure is stable. The concomitant diuretic dose should be reduced, if possible, to help minimize hypovolemia which may contribute to hypotension. (See WARNINGS and PRECAUTIONS, Drug Interactions.) The appearance of hypotension after the initial dose of ZESTRIL does not preclude subsequent careful dose titration with the drug, following effective management of the hypotension.

The usual effective dosage range is 5 to 40 mg per day administered as a single daily dose. The dose of ZESTRIL can be increased by increments of no greater than 10 mg, at intervals of no less than 2 weeks to the highest tolerated dose, up to a maximum of 40 mg daily. Dose adjustment should be based on the clinical response of individual patients.

Dosage Adjustment in Patients with Heart Failure and Renal Impairment or Hyponatremia: In patients with heart failure who have hyponatremia (serum sodium < 130 mEq/L) or moderate to severe renal impairment (creatinine clearance ≤ 30 mL/min or serum creatinine > 3 mg/dL), therapy with ZESTRIL should be initiated at a dose of 2.5 mg once a day under close medical supervision. (See WARNINGS and PRECAUTIONS, Drug Interactions.)

Acute Myocardial Infarction: In hemodynamically stable patients within 24 hours of the onset of symptoms of acute myocardial infarction, the first dose of ZESTRIL is 5 mg given orally, followed by 5 mg after 24 hours, 10 mg after 48 hours and then 10 mg of ZESTRIL once daily. Dosing should continue for six weeks. Patients should receive, as appropriate, the standard recommended treatments such as thrombolytics, aspirin, and beta-blockers.

Patients with a low systolic blood pressure (≤ 120 mmHg) when treatment is started or during the first 3 days after the infarct should be given a lower 2.5 mg oral dose of ZESTRIL (see WARNINGS). If hypotension occurs (systolic blood pressure ≤ 100 mmHg) a daily maintenance dose of 5 mg may be given with temporary reductions to 2.5 mg if needed. If prolonged hypotension occurs (systolic blood pressure < 90 mmHg for more than 1 hour) ZESTRIL should be withdrawn. For patients who develop symptoms of heart failure, see DOSAGE AND ADMINISTRATION, Heart Failure.

Dosage Adjustment in Patients With Myocardial Infarction with Renal Impairment: In acute myocardial infarction, treatment with ZESTRIL should be initiated with caution in patients with evidence of renal dysfunction, defined as serum creatinine concentration exceeding 2 mg/dL. No evaluation of dosing adjustments in myocardial infarction patients with severe renal impairment has been performed.

Use in Elderly: In general, blood pressure response and adverse experiences were similar in younger and older patients given similar doses of ZESTRIL. Pharmacokinetic studies, however, indicate that maximum blood levels and area under the plasma concentration time curve (AUC) are doubled in older patients, so that dosage adjustments should be made with particular caution.

HOW SUPPLIED

2.5 mg Tablets (NDC 0310-0135) white, round, biconvex, uncoated tablets identified as "ZESTRIL 2 1/2" on one side and "135" on the other side are supplied in bottles of 100 tablets.

5 mg Tablets (NDC 0310-0138) pink, capsule-shaped, biconvex, bisected, uncoated tablets, identified "ZESTRIL" on one side and "130" on the other side are supplied in bottles of 100 tablets and 1000 tablets, and unit dose packages of 100 tablets.

10 mg Tablets (NDC 0310-0131) pink, round, biconvex, uncoated tablets identified "ZESTRIL 10" debossed on one side, and "131" debossed on the other side are supplied in bottles of 100 tablets, 1000 tablets, 3000 tablets, and unit dose packages of 100 tablets.

20 mg Tablets (NDC 0310-0132) red, round, biconvex, uncoated tablets identified "ZESTRIL 20" debossed on one side, and "132" debossed on the other side are supplied in bottles of 100 tablets, 1000 tablets, 3000 tablets, and unit dose packages of 100 tablets.

30 mg Tablets (NDC 0310-0133) red, round, biconvex, uncoated tablets identified "ZESTRIL 30" debossed on one side, and "133" debossed on the other side are supplied in bottles of 100 tablets.

40 mg Tablets (NDC 0310-0134) yellow, round, biconvex, uncoated tablets identified "ZESTRIL 40" debossed on one side, and "134" debossed on the other side are supplied in bottles of 100 tablets.

Store at controlled room temperature, 20-25°C (68-77°F) [see USP]. Protect from moisture, freezing and excessive heat. Dispense in a tight container.

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ZENECA

Manufactured for:
Zeneca Pharmaceuticals
A Business Unit of Zeneca Inc.
Wilmington, Delaware 19850-5437
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F.P.O.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

19-777/S-037

Medical Review(s)

NOV 17 1999

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: NOV 17 1999

FROM: Robert Temple, M.D.
Director, Office of Drug Evaluation I, HFD-101

SUBJECT: Lisinopril mortality effect in CHF: the ATLAS study

TO: Raymond J. Lipicky, M.D.
Director, Division of Cardio-Renal Drug Products, HFD-110

Shaw T. Chen, M.D., Ph.D.
Team Leader (Medical), Division of Cardio-Renal Drug Products, HFD-110

The Chen/Hung review covers most of the relevant issues related to proposed new labeling for lisinopril. The reviewers conclude that the ATLAS study does not show that lisinopril has a mortality/morbidity outcome effect in patients with CHF who have not had a recent AMI. Lisinopril and several other ACE's (captopril, ramapril, trandolapril) have post-infarction (plus CHF or ventricular dysfunction) claims, but only enalapril (based on SOVD studies) has a non-infarct-related claim.

The ATLAS study had a formidable task, viz, showing superiority of a high dose of lisinopril to a low dose that provides some degree of effective ACE inhibition. Results clearly show that for its designated primary endpoint of overall survival, the study was unsuccessful. What is not so clear is whether the study shows a persuasive effect on one of the secondary endpoints. At one level, of course, the answer is "no;" they "spent their alpha" on the primary endpoint – but let's look anyway. This question is complicated by the presence of two sets of "secondary endpoints" and the apparent absence of any plan on how to use those endpoints. For the moment, let's consider the second group of endpoints. From the review, results on all endpoints were (Is the HR for CV mortality, CV hosp'n correct? It looks better than total mortality, CV hosp'ns, not worse):

	Endpoint	HD n=1568	LD n=1597	Hazard Ratio	Nominal p-value
1°	Total mortality	666 (42.5%)	717 (44.9%)	0.92	0.121-0.128
2°	Mortality, all hosp	1250 (79.7%)	1338 (83.8%)	0.88	0.001-0.002
	CV mortality	583 (37.2%)	641 (40.2%)	0.90	0.073
	All Mort., CV hospital	1115 (71.1%)	1182 (74.1%)	0.90	0.036
	CV Mort., CV hospital	1088 (69.4%)	1161 (72.9%)	0.91	0.027
	All MI, unstable Ang hospital'n	207 (13.2%)	224 (14.0%)	0.92	0.37

There is concern that these endpoints were developed late, perhaps with at least the knowledge that the primary endpoint had failed, but we have apparently not asked about this. Another problem plainly is what a true p-value might be, given the presence of 6 potential study endpoints. This is not a simple question;

5/6 of the endpoints have substantial overlap and are not in any sense independent. A Benferroni correction would therefore be highly conservative. The 6th endpoint (AMI plus angina hospitalizations) is much more independent, but is not a plausible one in light of past experience.

In retrospect, of course, the usual questions arise – why even have a secondary endpoint when it can't do any good? On the other hand, total mortality plus all hospitalization is a pretty familiar endpoint in CHF trials and the p-value is extreme (i.e., if there is any basis for looking at endpoints other than the primary, this one is pretty strong). The various other secondary endpoints (except AMI) are all directionally similar, albeit statistically weaker. One could say that only one of 5 secondary endpoints is reasonably strong and that correction would dilute this. On the other hand, the endpoints have highly overlapping (except AMI) components and are not independent. Indeed, one could say there are really only 2 endpoints: the mortality endpoint and the mortality plus hospitalization endpoint.

So, please consider approval further based on the following:

1. Total mortality plus total hospitalization is a standard endpoint.

2. The nominal p-value favoring lisinopril on that endpoint is quite small.

3. Other closely related endpoints (smaller event numbers) give essentially the same result; in fact, point estimates for all endpoints are similar.

4. Lisinopril has a post-MI outcome claim, perhaps additional pertinent information that would support reliance on a single study.

5. The control was probably somewhat effective, making the task of showing superiority in the study difficult. In particular, there is no reason to think the effect seen is unduly small.

I should add that I am very uncomfortable with the proposed solution: placing results in trials section but granting no claim. In this case the results can have no purpose except to give the claim. Indeed they would be the claim. I do not believe we can take this approach. Perhaps we could change the upper dose limit, but it's not easy to see the basis for that.

Robert Temple

Robert Temple, M.D.

cc:
Orig. NDA 19-777/S-037
HFD-110
HFD-110/Project Manager
HFD-101/R Temple
drafted:sb/11/12/99
final:sb/11/17/99
filename: Lisinopril_s037MM.doc

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
CDER/ODE-I/DIV CARDIO-RENAL DRUGS

Date: 10/25/99
From: Shaw T. Chen, M.D., Ph.D., Medical Group Leader, HFD-110
H.M. James Hung, Ph.D., Mathematical Statistician, HFD-710
Through: Director, Division of Cardiorenal Drug Products, HFD-110 OCT 26 1999
To: Director, Office of Drug Evaluation I, HFD-100

Subject: NDA 19-777/S-037, Lisinopril for Reducing Mortality/Morbidity in Heart Failure

Overview

The sponsor has submitted an efficacy supplement for NDA 19-777 (S-037), seeking approval of a new indication for Zestril (lisinopril) tablets [redacted]. This is a joint medical-statistical review of the submission.

Lisinopril is a non-sulfhydryl angiotensin converting enzyme inhibitor (ACEi) which has been approved for hypertension, improving survival after myocardial infarction, and management of heart failure. The last usage was based on an improvement in exercise tolerance and subjective symptomatology. The sponsor now presents results of a mortality/morbidity study *"Assessment of Treatment with Lisinopril and Survival* (the ATLAS Trial), to support the proposed new indication and benefit in heart failure. In addition, the ATLAS trial also attempted to address the issue of dose-response for ACEi in heart failure. The results of ATLAS have been described briefly at the 1998 Scientific Session of American Heart Association, but not yet formally published.

In the ATLAS, all patients were treated with open label 2.5-5 mg lisinopril and randomized to receive either 30 mg of double blind lisinopril or placebo. After a minimum of 3 year therapy, there is a statistically non-significant trend toward lower all-cause mortality (primary endpoint) for the high dose group and a nominally significant difference in combined mortality/morbidity favoring also the high dose lisinopril. The treatment effects were modest (8% for mortality and 12% in combined events). Thus, the study failed to distinguish the two doses in the strict statistical sense, but the secondary findings could not be easily ignored in view of prior experiences with ACEi in heart failure. The regulatory issues can be summarized as follows:

i) The ATLAS is a two dose comparison without concurrent placebo control.
ii) The treatment difference in primary endpoint did not reach statistical significance, although
iii) the secondary endpoint looked very good, and
iv) there are remarkable internal consistency across different endpoints and subgroups.
v) The magnitudes of the effects were modest, but in the ranges of other similar CHF trials.
vi) There are ample experiences with several members of the class that ACEi's have a mortality benefit in heart failure.

In addition to the ATLAS trial, the sponsor also submitted a study to demonstrate the bioequivalence of the 10 mg and 30 mg lisinopril tablets. The bioequivalence data will be reviewed by Dr. Parmelee of our biopharmaceutical staff.

The clinical trial description, dosage recommendation and related sections of the labeling for lisinopril have been edited. The Table of Contents starts on the next page.

Table of Contents

Background and History of Protocol Development

While the benefit of ACE inhibitor treatment in symptomatic heart failure has been clearly demonstrated, the dose-response relationship in such use is much less well-defined. There are some data suggesting that while the ACE related activities were independent of enalapril dose (5 vs 40 mg, Fowler et al, Circulation 98:I-854, 1998), improvement in non-mortality parameters may increase with dose (see cited references in protocol). The sponsor also asserted that lower doses of ACEi are usually prescribed in clinical practice than those used in clinical trials, without knowing the therapeutic values of the former. On the other hand, although several ACEi's have been shown to improve survival in CHF, mortality effects of lisinopril in the same setting have not been studied (and thus not labeled). The ATLAS protocol was therefore developed to compare two doses of lisinopril on all cause mortality in heart failure, with the hope of gaining approval . [ ]

The master ATLAS protocol was finalized on July 6, 1992 and submitted to the Agency on August 20, 1992. The protocol was revised later to refine the secondary endpoints and entry criteria (effective 4/9/93, submitted 8/5/93), and stipulate study termination/completion procedures (effective 11/15/96, submitted 3/6/97). The secondary efficacy endpoint were further changed by the Steering Committee on 3/15/97. The original set of 6 secondary endpoints were regrouped as 5 different ones (including two newly defined), with "combined all-cause mortality/hospitalization" as the *first* secondary endpoint. This new analytical plan was implemented on 12/9/97 (submitted to FDA 12/24/97), after the last patient completed the study on 9/4/97. There were no other interim protocol changes which might compromise the integrity of the study. In this memo, all protocol amendments are referred to by their submission dates.

The Claims

Based on the results of ATLAS trial, the sponsor has proposed to add the following new statement (the italics) in the indication for lisinopril:

[ ]

The proposed labeling also includes a description of the ATLAS trial and results in the section on "Pharmacodynamics and Clinical Effects", under the heading of "Heart Failure".

The ATLAS Protocol

The following description of the protocol is based on the original version and subsequent amendments, as presented in the supplement, which is not different from the copy submitted to the Agency earlier.

Title of Study:

Assessment of Treatment with Lisinopril and Survival (ATLAS).

Objectives:

To compare the effect of high and low doses of lisinopril on mortality and cardiovascular (CV) morbidity in patients with chronic congestive heart failure (Protocol Summary).

In the original main protocol, the Objectives were specified in more details, almost non-distinctive from that of study endpoints. They were further categorized as:
Primary Objective: comparing high and low dose effects on all cause mortality
and
Secondary Objectives: Comparing the two dose groups on:

1) Cardiovascular mortality due to:
   a) sudden death, b) CHF, c) myocardial infarction (MI), d) other reasons
2) Cardiovascular morbidity (hospitalization, emergency room/casualty visit for CV reasons
3) Combined all cause mortality and CV morbidity.
4) Combined CV mortality and CV morbidity.

The secondary objectives were revised in the amendment submitted 8/5/93 as follows:
- "other reasons" in 1)-d) above was changed to "other CV causes".

and add:
- "5) Incidence of non-fatal and fatal MI's"
- "6) Incidence of non-fatal and fatal MI's plus hospitalizations for unstable angina"

As noted above, further changes in the secondary objectives were recommended by the Steering Committee on 3/15/97. They were redefined as follows:

i) Combined all cause mortality and all cause hospitalizations
ii) Cardiovascular mortality
iii) Combined all cause mortality and CV hospitalizations
iv) Combined CV mortality and CV hospitalizations
v) Combined fatal/nonfatal MI and hospitalizations for unstable angina

These changes were implemented somewhat late in the course of the study (submitted to the Agency on 12/24/97), which did raise the suspicion that they were post hoc measures. Without breaking the blinding codes, they could have been revised after it became apparent that none of the original endpoints showed any treatment differences.

Study Design:
This is a multicenter, randomized, double blind, 2 parallel groups trial.

Investigators and Sites of Investigation:
Milton Packer, M.D. et al.
International and multicenter.

Number of Patients to be recruited:
1,500 Patients per group, 3,000 in total (see Sample Size Calculation). The protocol specified that the total number of patients to be admitted would be re-evaluated periodically by the Data and Safety Monitoring Board.

Inclusion Criteria: Male/female patients, 18 years or older, with the following will be enrolled:
- Clinical evidence of CHF, NYHA Class II-IV. Class II patients must have received treatment for CHF in past 6 months. CHF may be caused by either coronary artery disease or dilated cardiomyopathy.
- Documented left ventricular ejection fraction (LVEF) of $\leq$30% by radionuclide ventriculography or echocardiography. (Cineangiocardiography was added as a diagnostic