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®

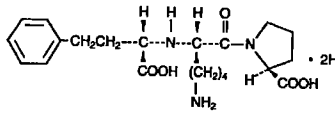
LISINOPRIL

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

technique for ejection fraction in the Amendment of 8/5/93)
The ejection fraction measurements must not be done within 2 months of an acute MI or cardiac surgery, or within 2 weeks of percutaneous angioplasty ("2 weeks" specified in 8/5/93 amendment).
- All patients must be treated with diuretics, with or without digoxin, for at least 60 days. Prior ACEi therapy was acceptable, but will be substituted with lisinopril at entry.
- Compliant with log-term follow-up (3-4.5 years).

Exclusion Criteria: Patients must not have any of the following:
- Unstable coronary artery disease. Defined as one of the following within 2 months before Visit 1: acute MI, severe/unstable angina, bypass /cardiac surgery. Or angioplasty within 2 weeks.
- Unstable ventricular arrhythmias. Defined as recurrent symptomatic ventricular tachycardia (VT), VT of at least 30 seconds in duration or with 24 hrs of an acute MI, or receiving antiarrhythmic agents with negative inotropic activity (flecainide, encainide, propafenone or disopyramide). [moricizine and flosequinan were later added to the list in the 8/5/93 Amendment.]
- Unstable heart failure. Defined as the presence of uncorrected hemodynamically significant primary valvular diseases, CHF requiring inotrope or ventilator support within 48 hrs before Visit 1, listed as waiting for cardiac transplantation.
- Any contraindication to the study drug. Including hypersensitivity, use of nonsteroidal anti-inflammatory (except for aspirin), serum creatinine >2.5 mg/dl.
- Concomitant life threatening disease with limited survival of <4.5 years.
- Severe pulmonary disease or serious psychiatric/personality disorders; history of substance abuse within 1 year.
- Participating in other CHF related trials.

Withdrawal Criteria: study medication and background therapy should be stopped for:
- Patient refusal to continue participation (but may be re-admitted if the patient agrees).
- Hospitalization for illness, cardiac or non-cardiac surgery.
- Cardiac transplantation.
- Serious adverse events, may be temporarily if event resolved and deemed not study drug related.
- Pregnancy.

The protocol also provided some instruction on how to manage the study drugs under certain clinical conditions (see below). In general, the investigators were advised to continue the study drug, unless "clinical judgement dictates otherwise". Thus the trial medications could be discontinued temporarily during the following intercurrent events:

i) Worsening heart failure (after adjusting, in the order of, diuretics, calcium blockers, digoxin, non-ACEi vasodilators and increase of open label lisinopril to 5 mg qd) requiring open label ACEi. Discontinuation may be permanent for recurrent, intractable instability of CHF.
ii) Acute MI. There were no automatic rules to stop the study drugs, only at discretion of the investigators.
iii) Worsening renal function (after adjusting, in the order of, diuretics, calcium blockers, non-ACEi vasodilators, decrease of open label lisinopril to 2.5 mg or 0 mg qd, and decrease of double blind medications).
iv) Symptomatic hypotension (after adjusting, in the order of, diuretics, calcium blockers, non-

ACEi vasodilators, decrease of open label lisinopril to 2.5 mg or 0 mg qd and decrease of double blind medications).

It was emphasized in the protocol that patients discontinued from study drugs (esp. those for worsening of CHF) must be followed to the end of study for final outcome analyses.

Randomization:

Randomization scheme was prepared centrally by [ ]

Dosage/Administration:

All patients were given open label lisinopril 2.5 or 5 mg once daily ("background therapy") throughout the study. During the initial 4-week dose-titration phase, patients also received 10 mg open lisinopril (added 2 weeks later for those who had never been treated with ACEi. After the run-in period, patients were randomized to 20 mg (for 2 weeks) then 30 mg double blind lisinopril or placebo. Dosage of the study medications may be adjusted downward later as described in "Withdrawal Criteria" above.

Compliance with dose administration would be documented with drug accountability.

Concurrent Therapies:

Concurrent with the study treatments, the investigators must follow standard practice regarding the uses of digitalis and diuretics. Patients may also receive beta-blockers, calcium channel blockers, short or long acting nitrates, hydralazine (or other vasodilators), warfarin (or other anti-coagulants) and aspirin. Acetaminophen will be used as an alternative to nonsteroidal anti-inflammatory drugs (NSAIDs).

During the course of this study, oral positive inotrope (except for digoxin), antiarrhythmic agents with negative inotropic effects, non-study ACEi, or NSAIDs (except for aspirin) will not be allowed.

Duration of Study:

After the 4 week run-in period, patients will be treated with the double blind study medication for 36-54 months.

Study Plan & Schedule of Assessment:

The study plan is summarized in Figure 1. Eligible patients entered a 4-week run-in period, receiving 2.5 mg or 5.0 mg lisinopril plus additional 10 mg open label lisinopril. (For patients not treated with ACEi previously, lisinopril must be started at 2.5 mg for at least one day and the open label 10 mg dose would be delayed for 2 weeks.) Other heart failure medications may be adjusted (as described above in "withdrawal criteria") in order to keep patients on 12.5-15 mg of lisinopril. Patients who could tolerate the above dose of open label lisinopril were further reviewed for inclusion/exclusion criteria at the end of run-in and randomized to double blind treatment of lisinopril 20 mg or matching placebo. Both groups remain on 2.5-5 mg of open label lisinopril after randomization and the double blind study medications would be increased to 30 mg after 2 weeks. Again, when dictated by the patients' clinical courses (see above in "withdrawal criteria"), other non-study medications would be adjusted first before changing the final dose of the study drugs. The efficacy endpoints would be assessed after 36-54 months of randomized double blind treatment (see below). Schedule and methods of assessments are summarized in Figure 2.

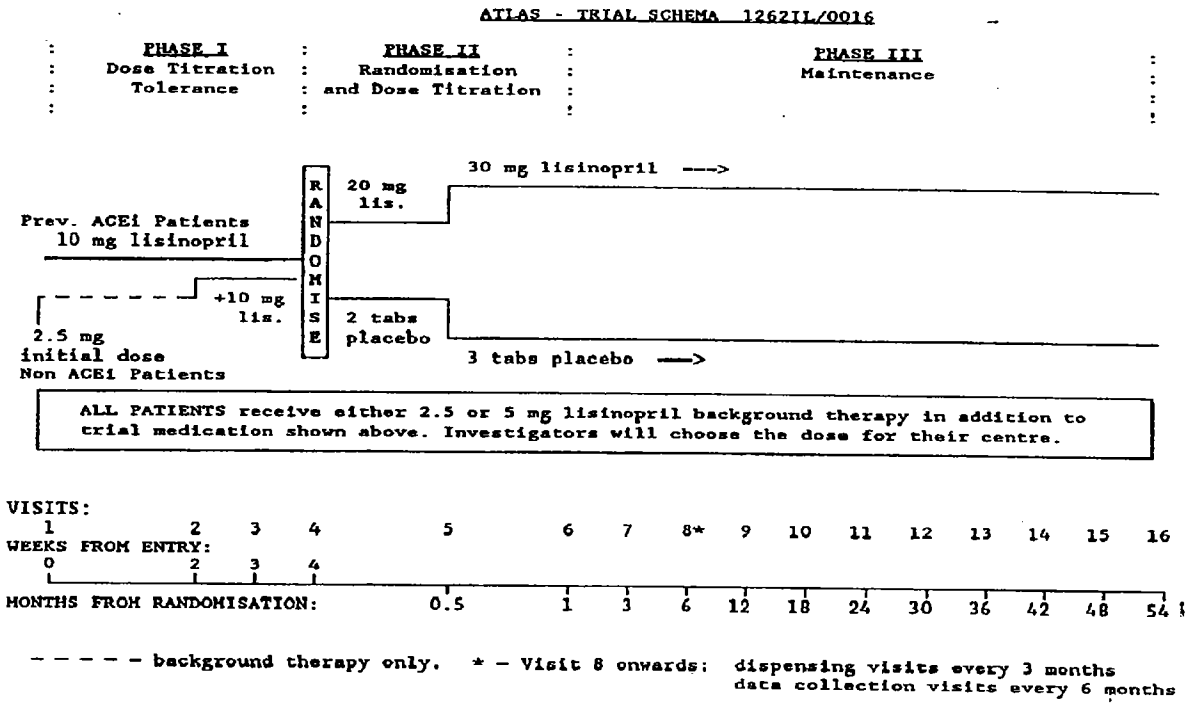


Figure 1. ATLAS Study Design

1262IL/0016 ATLAS : Assessment schedule

VISIT NUMBER	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
TIME FROM ENTRY (WEEKS)	0	2	3	4												
TIME FROM RANDOMISATION (MONTHS)				0	0.5	1	3	6	12	18	24	30	36	42	48	54
PROCEDURES;																
Inc/Exc/Consent	✓															
*Ejection fraction (≤30%)	✓															
Demography, aetiology/past medical history/physical exam	✓															
CXR/ECG	✓															
Cardiovascular examination/ clinical assessment	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Haematology/Biochemistry	✓												✓			✓
Clinical chemistry			✓		✓	✓	✓		✓		✓				✓	
Randomisation criteria/ compliance				✓												
**Medication dispensing	✓	✓		✓	✓	✓#	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Medication accounting		✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Adverse events		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

* Ejection fraction assessed by echo or radionuclide ventriculography within the 3-month period prior to or at visit 1
** Medication dispensing: dispensing visits after visit 8 will be every 3 months
# Not in US/Canada

Haematology/biochemistry will be assessed when the study is stopped or at visit 16, whichever is earlier

Figure 2: Schedule & Methods of Assessments.

Definitions of Efficacy Endpoints:

In this protocol, "Endpoint Definitions" (Section 7.1.8) only described the *components* of the endpoints. That is, combined endpoints to be analyzed were not defined here for "Definitions", but rather were included in the "Objectives" and "Statistical Analysis" (Section 9.3 of the original protocol). Thus, for purpose of efficacy analyses, the endpoints are listed under "The Objectives" above.

Primary:

All cause mortality at the end of the study.

For the pre-specified primary analysis, patients underwent cardiac transplantation would be considered as deaths related to heart failure.

Secondary:

Cardiovascular mortality.

The following details would be considered to classify the cause of deaths:

a) instantaneous death, witnessed or not, within a few minutes, with or without CHF or shock.

b) monitored arrhythmia leading to cardiac arrest.

c) unwitnessed death w/o preceding changes in symptoms nor ascribable cause.

d) stability of the patient's CHF prior to the terminal event.

e) For patients with severe CHF symptoms and death would be expected, the cause would be classified as due to CHF, even if the terminal event is arrhythmia.

f) For death due to acute MI, there must be symptoms and objective evidence of infarction (enzymes and ECG changes), and death occurs during hospitalization or within 28 days.

g) Other cardiovascular deaths include events such as stroke, pulmonary and peripheral thromboembolism, as well as deaths due to vascular procedures.

Cardiovascular morbidity.

Defined as non-fatal hospitalizations for cardiovascular causes. Other than mentioning acute MI and CHF as causes, there were no detailed definitions nor how the causes would be determined.

Case Report Forms:

In general, the blank Case Report Forms (CRF), as provided in Vol.14 of the submission, pages E1-E54, are adequately designed for collection of pertinent clinical data before and after randomization.

The study endpoints and patient status are recorded on Pages E46-E48 of the CRF, with the causes of deaths classified on Page E52. For non-cardiovascular deaths, the description was simple, but a page (E48) was reserved for autopsy report and narrative findings about the deaths. Documentation of acute ischemic events are provided on Pages E44-45, with adequate characterization instructions and a page for classification (E51).

During the study, changes in heart failure medications were allowed, including the study drugs (although as the last measure), but there is no space on CRF to document these changes.

Organization and Monitoring of the Study:

The study was conducted and monitored by the sponsor (Zeneca), with assistance from a Steering Committee and a Data and Safety Monitoring Board (DSMB). The membership and the duties of the two committees are described in Appendix III of the protocol.

The Steering Committee had the responsibility for the scientific and ethical integrity of the study and would prepare the final study report and publication. The members would not have access to blinded data during the study. All members will be independent of the sponsor, but ICI (Zeneca) will have two non-voting staff at all meetings of the Steering Committee. Of the list of its remits, it is not clear what constituted "Monitoring the analysis of the study".

The DSMB was charged with safety monitoring and would recommend to the Steering Committee on early termination of the trial for ethical (efficacy and safety) reasons. It would also monitor the sample size, advise on necessary adjustment in recruitment plan and establish written rules for early stopping. The DSMB was chaired by Prof. John Kjekshus of Oslo, Norway, and had 5 voting members. All DSMB members would be totally independent of the sponsor and other committees of the study, and would not include any ATLAS investigators. Summary of accrued trial data would be provided for the Committee at each of the meetings held every 6 months. Regulatory-wise, the only minor discomfort about DSMB is that the sponsor may send non-voting staff to the meetings.

According to the SAS database, there was an Endpoint Adjudication Committee. However, the study protocol did not describe such a group of experts who would review causes of death, reading of ECG/ echocardiogram, and assessment of other clinical events. Auditing of data integrity was described in the study report.

Sample Size Calculation:

The sample size calculation described in the study report is consistent with that in the protocol.

It was calculated that the study would need to enroll 3,000 patients (1,500 per group), based on the assumption that the all cause mortality would be reduced from 22.4% per year in low dose group to 19% per year in the high dose group (15% improvement) with a 90% power and two sided significance level of 5%.

Plan of Data Analysis:

All the efficacy endpoints are considered in terms of survival time of a particular event and will be analyzed on an intent-to-treat basis (analyzed as randomized). For any patient, if the event has not occurred at the time of analysis, the survival time will be calculated as the time from randomization to the date last known to be event free. The two doses will be compared using log rank test and Cox proportional hazard regression models, adjusted for prognostic factors (i.e., NYHA class and ejection fraction at randomization).

Additional analyses will also be performed to explore the possible interaction between the treatment effects of lisinopril at low or high dose and aspirin, and the possible relationship between the effect of lisinopril on mortality and the actual dose received.

There is no plan of interim analysis mentioned in the original or revised protocol. A Data and Safety Monitoring Board was established to formally review the study data at six-monthly intervals and possibly make a recommendation to the Steering Committee regarding continuation of the study. It was said in the original protocol that the DSMB would establish written stopping guidelines for the study at its early meetings. No document is available for the reviewers to determine when the stopping rule was decided in the DSMB meetings. According to Appendix H of the study report, four interim analyses were planned to occur after a minimum of 200, 400, 800 and 1200 deaths. The study report mentioned that the

stopping boundary was generated from O'Brien-Fleming alpha-spending function. Because of the interim analyses, the primary endpoint must have achieved a significance level of $p < 0.0394$ for it to be considered as producing statistically significant evidence of a difference between treatments. Corresponding to this adjusted significance level, a 96.1% confidence interval for the hazard ratio was presented.

Summary of Comments on the ATLAS Protocol:

The major problem with the ATLAS protocol is the lack of a true placebo control (i.e., no ACEi). At the time of study design for ATLAS (early 1992), it was probably considered unethical not to treat heart failure with ACEi, because of the findings from CONSENSUS and SOLVD trials. Nevertheless, while the study was designed based on the hypothesis that the higher dose (32.5-35 mg) of lisinopril was more effective than the lower dose (2.5-5 mg) in reducing mortality, there was a great risk that the results may be un-interpretable if the treatment differences between groups were not statistically significant. Even if there is a true difference between the doses, this difference may not be apparent in the final outcome because of the ATLAS design. While the patients would be randomized to the nominal doses of 2.5-5 mg or 32.5-35 mg, the protocol provided downward adjustment of double blind lisinopril from 30 to 20, 10 or 0 mg (see "Withdrawal criteria"). Thus the actually delivered dose range of the study may be contracted and render the between-group difference non-significant.

The sponsor also noted that there was a need to determine whether the doses of ACEi commonly prescribed by practicing physicians, which were substantially lower than that used in the CHF clinical trials, were also effective in improving the survival in heart failure. This question , however, cannot be answered by the ATLAS design even if the higher dose was shown to be superior to the lower one. No matter what the outcome of the ATLAS is, it would be impossible to know whether the low dose is superior to placebo. On the other hand, from a regulatory perspective, whether the low dose is effective is probably a moot point if the higher dose of lisinopril is shown to be superior to the lower dose. The high dose should then be recommended for general use because there are few dose-related safety issues, which is well-known for almost all ACEi's and can be tested again in this study of 3,000 patients.

The reviewers are concerned that the secondary efficacy endpoints were revised late in the course of the study (6 months before completion date, but *after* the last patient had completed the follow-up). Since the two treatment groups cannot be differentiated by the primary endpoint (see Efficacy Results), and the approvability of the new claim is dependent on the (revised) secondary endpoints, integrity of the latter data has become more critical. The reviewers did not find any evidence of unjustified code-breaking, but a substantial degree of suspicion remains. The original set of secondary endpoints need to be analyzed and compared with the outcomes of the revised definitions.

Another data dependent issue was the handling of patients lost to follow-up and without survival status, which has not been described prospectively in the protocol. According to the Study Report, this has not been a problem since all patients were followed to the end of study, there was not a single patient with missing efficacy data.

ATLAS Results: Patient Description

The ATLAS Study was completed in about five years, from 1992 to 1997. The results of the ATLAS trial were described in the Study Report of the submission, they have been published in seven articles. Copies of these publications are attached to this package.

All efficacy data presented in this memo are results of the reviewer's analyses, which were performed on the original data set submitted by the sponsor. In general, most of the data presented below are similar to that described in the sponsor's Study Report, any significant differences will be commented upon.

Patient Disposition:

Of 3,793 patients entered the trial, 3,164 were randomized in the double blind phase of the ATLAS Study. Reasons of rejection for the remaining 629 patients were (verified by the reviewers, see also Study Report Table 9):

LVEF >30% or not measured	33.2%
Adverse clinical or laboratory events	29.9%
Death	6.8%
Non-compliance (or <80%)	18.6%
Other administrative or no reasons	11.4%

Dispositions of 3,164 randomized patients are as follows:

	High dose	Low dose
Randomized	1,568	1,596
Withdrawal from treatment	426	489
Died	666	717
Survived	902	879

There appeared no missing patients whose survival status were not known at the end of the study. All patients were followed to the end of the study with respect to the mortality and morbidity outcomes, even for those with premature withdrawals.

As shown on table above, a total of 915 randomized patients had their double blind treatments permanently withdrawn during the study. The reasons are summarized as follows (verified by the reviewers, see also Study Report Table 10):

	High dose	Low dose
Withdrawals	426	489
Adverse events	267	287
Cardiac transplantation	3	1
Patient refused to continue	85	106
Administrative or no record	71	95

There is no remarkable differences in the numbers nor the distribution over time (Figure 3 of Study Report) of withdrawals for the two treatment groups. Discontinuations due to adverse events will be described in more details in the Safety sections. Non-compliance with protocol constituted the majority for other, administrative withdrawals.

Demographics and Baseline Characteristics:

The ATLAS study was conducted at 287 centers in the North America (US and Canada, 47% of the patients), Europe (16 countries, 50%) and Australia (3%). As summarized in Table 7 of the Study Report, the two randomized treatment groups were well-matched in their demographic and baseline characteristics. The ATLAS patient population were predominantly male (79-80%), white (>90%, 6-7% blacks) and older than 50 years (mean age of 64±10 yrs, 30-33% older than 70). The mean LVEF in ATLAS was 22.6±5.7% (maximum 30-33%) and a great majority of patients were in NYHA Class III (76-78%, 7% in Class IV). Ischemic heart disease (64-65%) was the most common etiology of CHF, fewer had cardiomyopathy (27-29%) or hypertension (19-21%). Before entering the study, 89% have received ACEi treatment, only a small portion (17%) received high dose of ACEi prior to randomization.

Protocol Violations/Deviations:

In the Study Report, "**protocol violations**" was defined as patients who did not satisfy the entry criteria, but were admitted to the study, and "**protocol deviations**" as those who did not comply with the protocol *after* entering the study. The sponsor claims to have performed all analyses on a strict intent-to-treat basis, thus no protocol violations or deviations were excluded in the efficacy assessment (including non-mortality data).

There were 113 **patients who should not have been entered**, 47 in the high dose and 66 in the low dose groups. The reasons, with more than one patient and in the order of decreasing frequency, were:

		High dose	Low dose
i)	on disallowed medications at entry	27	35
ii)	not on diuretics prior to trial	13	16
iii)	previous cardiovascular events outside time windows	8	14

The reviewers agree that the protocol violations were not significantly different between groups and inclusion of these few patient had no serious impact on the interpretation of data.

Only two conditions were reported as **protocol deviations**. They were evenly distributed in the two dose groups:

		High dose	Low dose
i)	on other ACEi during randomized treatment	180	200
ii)	extra open label lisinopril during randomized treatment	89	102

These protocol deviations may change the actual dosage difference between the groups, and thus affect the efficacy outcomes (see analyses below).

Concomitant Therapies:

In addition to the standard care for CHF (diuretics, digitalis and vasodilators/hydralazine), the most commonly (>1% of patients) used non-study drugs in the ATLAS were shown in the table on the next page (adapted from Table 14.1 of the Study Report and verified by the review team).

% of each group	at Randomization		Last visit	
	High Dose	Low Dose	High Dose	Low Dose
aspirin	40.5	40.4	39.8	38.7
anti-coagulants (warfarin)	35.8	35.5	40.0	41.7
nitrates (long acting)*	24.6	25.2	27.9	30.1
hypoglycemic agents	20.0	18.6	24.1	22.7
calcium channel blockers	11.7	11.7	14.4	15.9
beta blockers (all)	10.0	12.5	13.0	16.7
antiarrhythmics	9.0	10.4	15.5	14.1
anti-platelet (dipyridamole)	1.9	1.9	1.6	2.2
potassium supplement	1.4	1.8	0.7	1.0
NSAIDs	1.3	1.8	4.3	3.8
diuretics (all)	97.4	97.3	92.2	93.3
digoxin/digitalis	66.8	67.5	66.1	69.7
vasodilators (hydralazine)	42.6	43.9	45.8	49.3
extra ACEi	0.1	0.4	12.0	14.6

* similar numbers for short acting nitrates

Use of these concomitant medications were not significant different between the two treatment groups and increased slightly over the course of the study, probably reflect the nature of a chronic, progressive disease. It should be noted that extra-doses of open label ACEi (a protocol deviation) were prescribed increasingly from nearly zero to 12-14% over 3-4 years, but diuretics were administered less frequently at the end of the study (from 97 to 92%).

Differential treatment outcomes by concomitant medications are presented in Tables A.1 and A.2 (see Efficacy Results below).

Dosages and Adjustment of Randomized Treatment during Study:

While changing the dose of blinded randomized study drugs was discouraged in the protocol and should be done after adjusting other heart failure medications first, the dosages of double blind lisinopril were reduced for many patients in both groups, the percentages of patients receiving no blinded study drugs increased from 2 and 1% (High and Low dose) at randomization to 32 and 35% (High and Low dose) at the end of the trial (see Figures Z1.13 to 1.18 of the Study Report). The data also indicated that these dose adjustment were made early in the study for most patients (e.g. at Visits 3 or 4). Throughout the course of the study, relatively few received intermediate doses of 1-2 tablets (at the last visit, 8% in High dose and 5% of Low dose).

Despite that all patients should remain on 2.5-5.0 mg of open label lisinopril, specified as background therapy in the protocol, substantial numbers of patients (27% of High dose and 31% of Low dose) did not receive any lisinopril (open label or blinded) at the last visit (see Figure on dose distribution in Safety). Some of these patients may have received poorly documented (and protocol-deviated) open label ACEi. Because the "total dose" of lisinopril in the low dose group actually included both the number of placebo tablets and the open label lisinopril (background therapy), the "actual dosage" for that group was neither all of lisinopril nor placebo. This may not be as confusing if the low dose group can be distinguished from the high dose one.

Another potentially confounding problem is the use of extra ACEi in addition to the background therapy and the randomized study drugs (in 12-15% of patients, see Table above), some of these non-protocol ACEi's were not lisinopril. Thus the accumulated ACE inhibition from these agents and the contribution of these protocol deviations to the treatment effects are difficult to estimate.

As the result of provision for dose reduction in the protocol, the mean dosages of total lisinopril decreased from 33.2 mg/4.5 mg (High/Low dose groups) at randomization to 22.5 mg/3.2 mg at the end of trial (the last dose recorded for each patient) (from Table 24 of the Study Report).

Compliance and Duration of Treatment:

There was no information on the compliance of study drug administration in the Study Report. The durations of treatment were described in more details in the Safety Sections. There is no between-group difference in total number of patient-years exposed to the study drugs.

ATLAS Results: Efficacy Data

All efficacy results presented below were based on the Agency's own statistical analyses of original data submitted by the sponsor. Contents of the sponsor's study report are, generally, in good agreement with this review, discrepancies will only be commented upon when appropriate.

Primary Efficacy Endpoint:

For **all cause mortality**, patients randomized to high dose lisinopril had numerically fewer deaths than those of the low dose group (reviewers' analyses shown below, which are similar to that presented in the sponsor's Study Report):

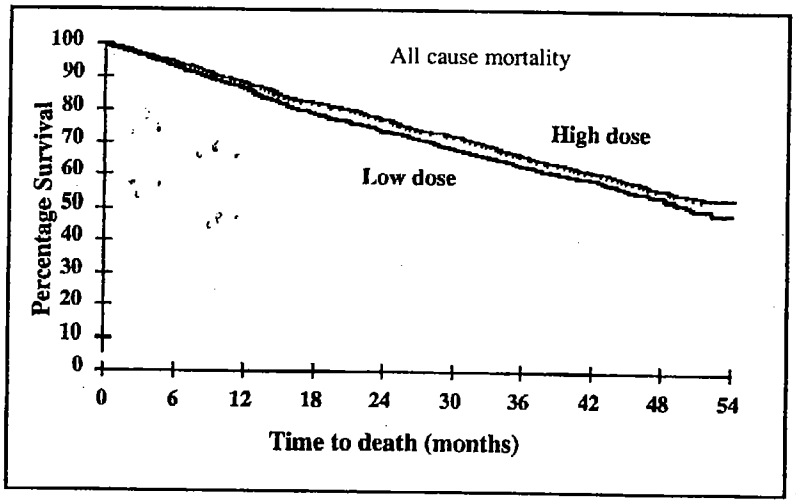
Primary Endpopint: All Cause Mortality	High Dose (N=1568)	Low Dose (N=1596)
Deaths	666 (42.5%)	717 (44.9%)
/1000 pt yrs	141.4	153.7
Hazard Ratio (H:L)	0.921	
(96.1% CI)*@	(0.825-1.029)	
risk reduction	7.9%	
p (log rank)*@	0.128	
p (log rank)*$	0.121	
Median (months) to event	56.2	52.1

* adjusted for planned interim analyses, significance threshold is p<0.0394

@ adjusted for NYHA Class and LVEF.

$ not adjusted for the covariates.

However, the difference is not statistically significant (with threshold of p<0.0394, adjusted for interim analyses). The Kaplan-Meier survival curves are shown below:



Nearly 90% of all deaths were due to cardiovascular causes, as determined by the Endpoint Committee, which also accounted for the difference in total mortality between the two dose

groups (see Study Report Table 15).

Included in the primary mortality analysis were 39 cases (19 on high dose, 20 on low dose) of cardiac transplants. Excluding or censoring of these patients did not change the difference in outcomes between the two dose groups.

Results of Interim Analyses

The results of the 4 interim analyses on all cause mortality is given in the following table. None of the 4 interim analyses achieved significance and the trial continued.

Interim analysis	Proposed number of deaths	Actual number of deaths	Log-rank test: critical value for early stopping	Actual Log-rank value	Significance level for early stopping	Actual significance level
1	200	234	3.5	0.9	0.00047	0.33
2	400	407	3.2	1.4	0.00127	0.17
3	800	814	2.9	1.7	0.00334	0.08
4	1200	1149	2.7	1.6	0.00522	0.11

From Appendix H of the study report, the combined endpoint of all-cause mortality and all-cause hospitalizations, all-cause mortality and CHF related hospitalizations, number of hospitalizations, number of CHF hospitalizations, number of cardiovascular hospitalizations, number of ischemic hospitalizations, number of outpatient visits, and ten most frequent reasons for hospitalizations were examined during the interim analyses (Sponsor's Tables H27.1-27.4, H28.1-28.5, H29.1-29.2). All these analyses might, directly or indirectly, have an impact on the decision of choosing the combined all-cause mortality and all-cause hospitalizations as the most important secondary endpoint by the Steering Committee.

All Cause Mortality: relations with actual dose received

As described above, the actual doses of blinded lisinopril were adjusted during the study which resulted in a smaller difference in mean dose between the two treatment group. The sponsor performed proportional hazard regression analysis to report that *mean actual dose* had a statistically significant effect (nominal $p < 0.001$) on all-cause mortality, the estimated hazard ratio for a 1 mg increase in dose being 0.993 (95% confidence interval 0.989 to 0.997). We explored possible relationship between incidence of all-cause mortality and *the last dose* taken, as described in the following table.

Incidence of all-cause mortality by last dose taken

	2.5 mg	5 mg	10 mg	15 mg	20 mg	25 mg	30 mg	32.5mg	35mg	65 mg
N	301	120	61	74	11	839	14	237	1482	25
%	45%	44%	36%	50%	27%	43%	43%	45%	44%	36%

The proportional hazard regression analysis does not suggest any possible relationship between incidence of all-cause mortality and last dose taken, the hazard ratio being 1.00 (namely, trend is perfectly flat). The p-values from such analyses (ie, incidence of endpoint

vs. mean dose or last dose) are difficult to interpret because of many inherited unverifiable assumptions, such as, all last dose groups are statistically independent because of randomization. Thus we elect not to report the p-value.

All Cause Mortality: subgroup analyses

The small **mortality** difference between the two doses of lisinopril treatment was fairly consistent across many **subgroups** in demographics, baseline characteristics and concomitant medications (Table A.1, reviewers' analyses). Relative risks were mostly close to one and numerically in favor of the high dose group regardless of NYHA class, LVEF, use of (extra) ACEi and use of aspirin. For other patient characteristics with differences in the opposite direction (more deaths in the high dose group), the numbers of subjects were small and the relative risks were of wide confidence intervals. In any case, the differences were not big enough to indicate that either dose of lisinopril had a relatively adverse effect on survival in these subgroups (all 95% confidence intervals for relative risk contain one).

Secondary Efficacy Endpoints (revised):

Results of analyses on the new set of secondary endpoints (described above in Objectives of the protocol) are described below. It should be reiterated that the reviewers are concerned that the secondary efficacy endpoints were substantially revised relatively late in the course of the study and we have thus performed additional analyses based on the original definitions of secondary endpoints (see below).

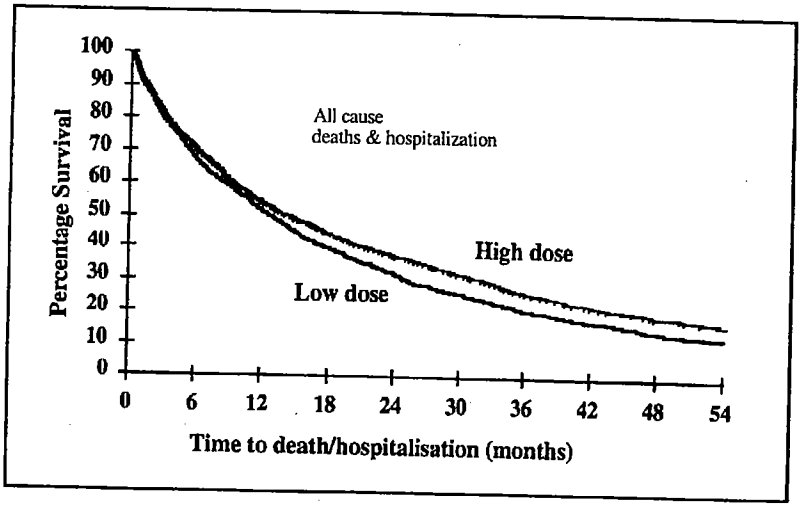
Consistent with the trend in primary endpoint, all secondary endpoints also favored numerically the high dose group. Some of which reached nominal p values of <0.05. The most prominent difference was seen in **combined all cause mortality and all cause hospitalization**:

Secondary Endpopints: All Cause Mortality/Hospitalizatio	High Dose (N=1568)	Low Dose (N=1596)
Events	1250(79.7%)	1338(83.8%)
/1000 pt-yrs	472.6	548.0
Hazard Ratio (H:L) (95% CI)	0.884 (0.818-0.955)	
risk reduction	11.6%	
nominal p (log rank)@	0.002	
nominal p (log rank)$	0.001	
Median (months) to event	14.5	12.9

@ adjusted for NYHA Class and LVEF.

$ not adjusted for the covariates.

For this endpoint, the Kaplan-Meier survival curves (shown below) started to separate increasingly after 6 months of treatment.



Similar to that observed for the primary endpoint of all cause mortality, the results of this revised secondary endpoint were not related to the **actual *last dose*** **received**. The estimated hazard ratio was 1.00 (namely, the trend is perfectly flat):

Incidence of all-cause mortality and all-cause hospitalizations by last dose taken

	2.5 mg	5 mg	10 mg	15 mg	20 mg	25 mg	30 mg	32.5mg	35mg	65 mg
N	301	120	61	74	11	839	14	237	1482	25
%	82%	84%	79%	85%	64%	82%	86%	84%	81%	84%

For this combined endpoint, responses in many **subgroups** in demographics, baseline characteristics and concomitant medications were remarkably consistent. The treatment differences were not only numerically in favor of the high dose group, but also with narrow confidence intervals excluding one (Table A.2, reviewers' analyses). The only exception is a opposite numerical trend in the subgroup of patients receiving calcium channel blockers, but the number of patients was small (183) and the confidence interval encompassed one.

Results of other secondary endpoints are summarized as follows:

Secondary Endpopints: Events (%)	High Dose (N=1568)	Low Dose (N=1596)	risk ratios	(95% CI)	nominal p (log rank)
Cardiovascular (CV) mortality	583(37.2%)	641(40.2%)	0.90	(0.81-1.01)	0.073
All deaths+CV hospitalization	1115(71.1%)	1182(74.1%)	0.90	(0.84-0.99)	0.036
CV deaths+CV hospitalization	1088 (69.4%)	1161(72.7%)	0.91	(0.84-0.99)	0.027
All MIs + Unstab angina hosp	207(13.2%)	224(14.0%)	0.92	(0.76-1.11)	0.37

Of these secondary endpoints, it is interesting to note that the treatment effect on MIs and related events was the smallest. One may recall that ACEi had not been shown to reduce recurrent MIs in previous studies of post infarction patients (e.g., SAVE, AIRE, GISSI-3 Studies etc).

Secondary Efficacy Endpoints (original):

Of the 6 original secondary endpoints, 4 were retained in the revision (see results above) and the remaining 2 (Fatal and non-fatal MIs, Cardiovascular mortality) were excluded from the final list of secondary endpoints. The reviewers have performed analyses on the two original but excluded secondary endpoints, the results are shown in the table below:

Secondary Endpopints: Events (%) (original)	High Dose (N=1568)	Low Dose (N=1596)	nominal p (log rank)
Fatal and Nonfatal MI	122 (7.8%)	139 (8.7%)	0.26
Cardiovascular Mortality	583 (37.2%)	641 (40.2%)	0.073
Sudden death	286 (18.2%)	303 (19.0%)	
Cardiac transplantation	19 (1.2%)	20 (1.3%)	
Myocardial (Heart) failure	184 (12.9%)	222 (13.9%)	
MI related	52 (3.3%)	45 (2.8%)	
Other cardiovascular	42 (2.7%)	51 (3.2%)	

None of these two original secondary endpoints showed any treatment differences with a nominal p value of less then 0.05. The results described above are based on the endpoints adjudicated by the Endpoint Committee, classification by investigators gives similar findings.

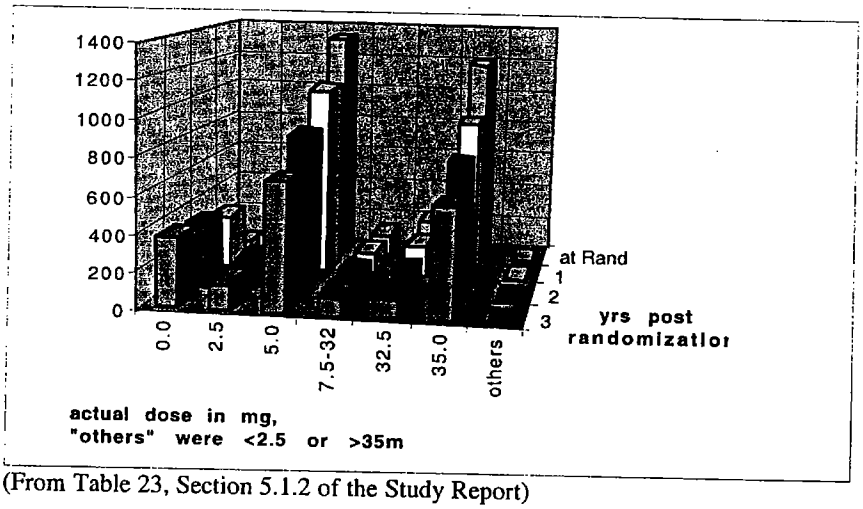
ATLAS Results: Safety Experiences

The safety data of ATLAS study provided a rare opportunity to look at the dose-relations of long-term adverse effects for lisinopril. In general, all adverse events reported in ATLAS were already known for lisinopril and differences from previous experience with the drug (in other patients populations) were more of quantitative and severity nature.

Extent of Exposure

Subjects in ATLAS were exposed to lisinopril for total of 4709 patient-years in the high dose group and 4665 patient-years in the low dose group.

The distribution of patients on actual dose is shown in the figure below for all randomized patients over the course of the study. In the following diagram, most, but not all, of the patients received low actual doses (≤ 5mg) were randomized to the Low dose group and vise versa for the high dose patients (because patients randomized to low dose may received extra ACEi in deviation of protocol). As described above in Dosage & Adjustment, blinded therapies were totally withdrawn for more and more patients over time (32-35% at the last visit). There was no significant between-group difference in this change.



(From Table 23, Section 5.1.2 of the Study Report)

The overall treatment durations and the mean doses are shown as follows (from Figures Z1.13-Z1.17 and Table 24 of Study Report):

	End of Titration	1 year	2 years	3 years	4 years
High dose (N=1568)	1560(99%)	1379(88%)	1209(77%)	1036(66%)	324(21%)
mean dose (mg)	33.2	28.9	27.3	26.0	25.2
Low dose (N=1596)	1584(99%)	1379(86%)	1183(74%)	1011(63%)	327(20%)
mean dose (mg)	4.5	4.1	4.0	3.7	3.4

Again, in the above table for treatment duration, note that the dosages are varied within the groups and over the years. While the mean doses decreased over time, more than half of the patients remained at the randomized dose (see median doses in Table 24 of Study Report).

Overall Adverse Experiences

In this heart failure trial, adverse events were reported in more than 90% of patients, similarly in both treatment groups (94.5% vs 96.1%, high vs low dose). Of these, 79%/83% (High/Low dose) were considered serious, 17%/18% led to withdrawals, and 42%/34% were classified as drug related. While there is no between-group difference in overall incidences (overall, serious, or leading to withdrawal), more adverse events were attributed to the study drug in the high dose group.

All Adverse Events

There were no unexpected, alarming new adverse events reported in this study and the profiles of adverse experiences are similar in either dosage group (Table 26 of Study Report). Of those with >5% rates, the following occurred more frequently (by nearly 2% or greater) in the high dose group (ranked by the difference):

% of patients Events	High dose (N=1568)	Low dose (N=1596)
dizziness	18.9	12.1
hypotension	10.8	6.7
Cr increased	9.9	7.0
hyperKalemia	6.4	3.5
NPN* increased	9.2	6.5
syncope	7.0	5.1

* non-protein nitrogen

It is interesting to note that some of the signs/symptoms related to volume/renal effects of ACEi were reported more frequently in the high dose group. This dose-relationship in adverse experiences has rarely been described in the past, probably because long-term dose ranging studies were infrequent for ACEi in various indications.

On the other hand, the following adverse events related to heart failure occurred more commonly in the low dose group, probably reflecting the relative efficacy in CHF morbidity for the two doses:

% of patients Events	High dose (N=1568)	Low dose (N=1596)
dyspnea	18.1	22.3
CHF*	23.9	26.3
heart failure*	14.0	18.2
cough increased	10.6	13.2

* COSTART system designation

Other adverse events, which were reported in 5% or more patients of either group, but had no remarkable differences (by <2%) between the two doses, are summarized in the following table (ranked by the incidence in the high dose group). Without a placebo (or other control) group, it is impossible to place any meaning on these findings.

% of patients Events	High dose (N=1568)	Low dose (N=1596)	% of patients Events	High dose (N=1568)	Low dose (N=1596)
chest pain	14.9	15.6	diarrhea	6.2	6.4
sudden death	14.3	14.8	kidney func abn	6.1	4.5
pharyngitis	13.0	14.1	nausea	5.9	6.8
angina pectoris	12.3	13.6	kidney failure	5.5	5.3
asthenia	10.7	10.6	UTI	5.5	4.4
pain	9.8	9.2	flu syndrome	5.4	4.4
bronchitis	9.0	9.6	back pain	5.3	5.4
pneumonia	8.1	9.8	diabetes mellitu	4.9	5.1
gout	7.5	8.1	periph edema	4.8	5.1
MI	7.1	7.3	heart arrest	4.6	5.9
abdominal pain	6.5	6.9	rash	4.6	5.8
atrial fibrillatic	6.3	6.7	unevaluable	4.5	5.4

Deaths

There was no between-group imbalance in total mortality or non-cardiovascular deaths that may raise a safety concern. The former has been discussed in details as a primary efficacy endpoint. For non-cardiovascular death, it occurred in 4.8% in the high dose group and 4.4% in the low dose group. The most common causes were sepsis, neoplasm and pneumonia.

Events Leading to Withdrawal

Of the randomized patients, 17.5% (17% high dose, 18% low dose) were withdrawn for adverse experiences. Except for heart failure, most specific reasons were in the ranges of less than 1%. For those withdrawals due to ACEi related events, all were infrequent in both groups:

% of patients Withdrawals	High dose (N=1568)	Low dose (N=1596)
cough increased	0.9	0.9
hypotension	0.8	0.6
kidney failure	0.7	0.8
NPN* increased	0.6	0.4
kidney func abn	0.4	0.6
hyperKalemia	0.4	0.1
dizziness	0.3	0.0
Cr increased	0.3	0.4
syncope	0.3	0.3

* non-protein nitrogen

Patients were also withdrawn for the following reasons related to heart failure, and again, only minor differences were noted between groups:

% of patients Withdrawals	High dose (N=1568)	Low dose (N=1596)
CHF*	3.2	3.1
heart failure*	0.8	1.7
dyspnea	0.6	0.5
lung edema	0.2	0.4

* COSTART system designation

Overall, pattern of reasons for withdrawal in ATLAS patients was not too different from that of lisinopril (non-mortality) heart failure trials. Except for CHF, discontinuations due to other clinical events were as rare as in previous experiences.

Serious Adverse Events

Serious adverse events were reported in 79% of the high dose group and 83% of the low dose group. The following table lists those serious events with 5% or greater incidences (ranked by the difference):

% of patients Serious Events	High dose (N=1568)	Low dose (N=1596)
heart failure*	11.9	16.2
dyspnea	7.5	10.4
CHF*	20.3	22.8
pneumonia	6.4	7.9
angina pectoris	8.6	8.9
chenst pain	7.7	8.0
MI	6.8	7.0
sudden death	13.4	13.6

* COSTART system designation

These serious events were reported more frequently in the low dose group, especially those related to heart failure. Less common (>1% and <5%) but occurred in more or less frequently in the high dose group (vs low dose group, by at least 1%) are shown below (ranked by the difference):

% of patients Serious Events	High dose (N=1568)	Low dose (N=1596)
VT	4.5	2.9
hypotension	4.8	3.2
syncope	4.8	3.6
heart arrest	4.5	5.8
CVA	3.3	4.6
lung edema	2.9	4.4

Of the above, ventricular tachycardia, hypotension and syncope were reported more frequently in the high dose group.

Laboratory Tests and Vital Signs

Changes in hematology, hepatic and renal chemistry, as well as vital signs, are presented in Sections 5.8 and 5.9 of the Study Report. As expected, patients with severe systolic hypotension had higher mortality, but not excessively in the high dose group (see Table 18 of the Study Report). There were no surprising findings nor remarkable differences between the two dose groups in these safety parameters.

Demographic Differences

For all adverse events, serious and leading to withdrawals, there appeared to be no distinctive difference between the two doses in demographic subgroups of age, gender and race, although

the numbers of racial minorities in ATLAS were too small. However, for those adverse events considered by the investigators to be *drug related*, there appeared to be a wider dose difference (more reports in the high dose group) in the elderly (≥ 70) and male (see Study Report Table T15.1, amended 10/19/99).

Regulatory Issues

A. *Did the study find anything?*

While the ATLAS Trial was reasonably designed (see Summary of Comments on Protocol above) and well-executed without loss of follow up data, the two doses of lisinopril were not distinguishable statistically in the **primary endpoint** of all cause mortality. The small numerical difference in total deaths in favor of the high dose group has a p value of 0.128 and was similar in different demographic and clinical subgroups. The failure to reach statistical significance might be due to a lower event rate (approximately 15% mortality per year) and a smaller treatment effect (8% risk reduction) than those estimated for sample size calculation (22% mortality per year and 15% improvement from low to high dose). The smaller treatment effect in primary endpoint might in turn be a consequence of the contraction in dose range from the nominal 32.5-35 mg vs 2.5-5 mg at randomization to mean actual doses of 22.5 mg vs 3.2 mg at the last visits (downward dose adjustment allowed in protocol, see above), as well as the blurring of the dose differences by undocumented extra ACEi received in some patients. Post-hoc analyses based on the *mean actual dose* appeared to suggest that mortality may possibly be dose-related (see above). However, analyses based on *the last actual dose* did not confirm this dose-relationship.

While the study was not positive in a statistical sense and thus no definitive conclusion can be drawn from any of the efficacy analyses, the results of the (revised) **secondary endpoints** are consistent with the numerical trend of the primary endpoint and provided some hints that the high dose lisinopril might be more effective than the low dose. With a higher background event rate in the combined endpoint of **all cause mortality plus all cause hospitalizations**, the high dose treatment had a risk reduction of 12% over the low dose, with a nominal p value of 0.002. Results of other secondary endpoints were similar (with more marginal p values), but not providing any additional support because they were not truly independent (e.g. cardiovascular deaths plus cardiovascular hospitalizations). Based on the reviewers' analyses, the treatment differences in the two original, but later excluded, secondary endpoints were also not significant with nominal p of >0.05 (all MI's: p=0.26, CV deaths: p=0.073).

It is probably worth noting that the magnitudes of risk reductions appeared to be similar (about 8-10%) across almost all endpoints.

The review team concluded that the failure of the ATLAS trial to distinguish the two doses of lisinopril might be the results of statistical misfortune in the estimate of even rates and a narrowed dose range, rather than due to intrinsic pharmacology of lisinopril (see discussion below). The study seemed to suggest a possible difference between the two doses of lisinopril, but the results of the secondary endpoint per se were not convincing enough to support a bona fide new indication.

B. ***What does the finding mean?***

Since many ACE inhibitors have been approved by this Agency for treatment of heart failure, some with claims of mortality benefits, it is difficult not to consider all previous related studies and put the ATLAS results into perspective of current understanding. Prior to ATLAS, lisinopril has been shown, and approved for such indications, to confer symptomatic benefits in congestive heart failure and to improve survival in post acute MI patients (not necessarily in heart failure). While the patient populations are not identical in these two different clinical settings, they are not totally unrelated.

Currently, of the 9 ACEi on the U.S. market, 7 carry approved indications for heart failure and 5 of which have been shown to improve survival^. The results of 5 placebo controlled mortality trials are compared with that of ATLAS in the following table:

Mortality Trials ACEI	Studies	Diagnosis	size	durations	Mortality (%) ACEi vs Contro	risk reduct.	(p)	morbidity risk reduc.*
captopril	SAVE	CHF s/p MI	2231	2-5 yrs	20.4 vs 24.6	19%	0.02	22%
enalapril	SOLVD-T	CHF	2569	2-4.5 yrs	35.2 vs 39.7	16%	0.007	30%
ramipril	AIRE	CHF s/p MI	2006	2 yrs	16.9 vs 22.6	27%	0.002	26%
trandolapril	TRACE	CHF s/p MI	1749	2 yrs	29.8 vs 35.3	16%	0.042	20%*
lisinopril	GISSI-3	all MI	19394	6 weeks	6.4 vs 7.1	11%	0.04	#
lisinopril	ATLAS	CHF	3164	3-4.5 yrs	42.5 vs 44.9	8%	0.128	24%

\# open label and smaller than missing data

* hospitalizations for CHF, except for trandolapril (combined endpoint)

Thus one may argue that in view of the past experiences with other ACEi's and the results of GISSI-3 for lisinopril, as well as consistent symptomatic benefits for 9 members of the class, it is inconceivable that lisinopril would be clinically different from other ACEi and would not improve survival in heart failure. The results of the secondary endpoint in ATLAS, a rather solid one of combined all cause mortality and hospitalizations, appeared thus to be more believable than that in an isolated trial which failed on the primary endpoint. However, not all placebo-controlled mortality trials of ACEi were positive. For various reasons, the numerical trend favoring ACEi over placebo did not reach statistical significance in CCS-1 (captopril) and SMILE (zofenopril), and the treatment difference was even in the wrong direction for enalapril in CONSENSUS-2 (all post acute MI studies):

Mortality Trials ACEI	Studies*	Diagnosis	size	durations	Mortality (%) ACEi vs Contro	remark
captopril	CCS-1	MI	13634	4 wks	9.1 vs 9.6	
enalapril	CONSENSUS-2	MI	6090	6 ms	11.0 vs 10.6	started w/iv for 24 hrs
zofenopril	SMILE	MI	1556	6 wks	4.9 vs 6.5	10% vs 14% at 1 yr

* all placebo controlled, oral treatments (iv for CONSENSUS-2) started within 24-36 hrs of MI.

^ For survival claims, only enalapril was tested in heart failure patients not necessarily post acute MI. Captopril, ramipril and trandolapril were all studied in CHF patients suffered a recent MI (within a few days). As noted above, lisinopril has been shown to improve survival in post acute MI patients, who may or may not have left ventricular dysfunction (GISSI-3).

Thus, without a concurrent placebo control, we really do not know where the results of ATLAS stand. The overall evidence therefore remains circumstantial at best and does not provide the same statistical support as the mortality data of other ACEi trials. It will therefore be unfair to approve, on the basis of ATLAS and all the background information, a brand new mortality indication for lisinopril. Instead, the findings of ATLAS should only be described in the clinical trial section of the labeling, indicating that a higher dose of lisinopril might have some mortality/morbidity benefit in heart failure over a lower dose. But the evidence is inconclusive and the inference relies in part on prior experiences with lisinopril and other ACEi's. The language of current indication (management of heart failure should remain unchanged.

C. *Can we write instructions for use?*

Since lisinopril is already approved for management of heart failure, the question is whether the ATLAS data have provided new information about which dose to use (2.5-5 mg vs 32.5-35 mg) to improve both the efficacy and safety outcomes of lisinopril. The current recommended daily doses for lisinopril are 5-20 mg for heart failure and 5-10 mg for post acute MI.

For efficacy, again, there was a hint, but no solid evidence, that high dose of lisinopril at 32.5-35 mg might be more effective in reducing the risk of mortality/morbidity in heart failure. This dose may be reduced for safety reasons (blood pressure, renal function and fluid status), as stipulated in the ATLAS protocol. In fact, doses of lisinopril were indeed decreased for many patients (about one third randomized to high dose received no blinded lisinopril, apparently for tolerability problems). It can not be concluded from ATLAS that the low dose lisinopril (2.5-5 mg) was significantly better than placebo.

Contrary to the usual belief that ACEi's have no dose related adverse reactions, the safety experience from ATLAS suggested that adverse events associated with the pharmacology of ACE inhibition (hypotension and related phenomena, renal function and fluid status) were slightly more common in the high dose group. However, most of these adverse experiences were not serious and more of tolerability issues than significant safety concern of irreversible harm. Thus, there is no safety reason not to start the dose at 32.5-35 mg, and titrate accordingly as described above.

In this respect, one may argue that the ATLAS data were inadequate to support a new indication, but may provide some new dosage information.

D. Other Regulatory Considerations

Since lisinopril has been approved for management of heart failure and has been shown to improve survival in the post acute MI setting, approval or non-approval of the new claim in heart failure has no practical impact on the public access to the treatment or physicians' prescribing behavior in managing CHF. There are several other ACEi's also available for the same indication, which have stronger evidence of mortality benefit. On the other hand, regulatory outcome of this application will have minimal implication on further research in the same clinical setting.

Conclusions

The ATLAS data seemed to suggest that lisinopril treatment at 32.5-35 mg once daily might be more effective than the low dose (2.5-5 mg) regimens in reducing the risk of mortality/morbidity in heart failure. The new information was not strong enough to support a new claim in chronic CHF (without recent MI), but may allow use of lisinopril at a higher dose than that currently recommended (5-20 mg) in the management of heart failure.

It is recommended that the current indication of lisinopril for management heart failure should not be changed. The study and results of ATLAS may be described in the clinical trial section and the dosage recommendation for CHF increased to 35 mg.

Shaw T. Chen, M.D.,Ph.D.

H.M. James Hung, Ph.D.
statistical review concurred by:
Dr. Chi

cc:
ORIG: NDA- 19-777/S-037
HFD-110
HFD-110/McDonald
HFD-710/Hung/Chi
HFD-110/SChen/10/25/99

Table A.1 All cause mortality by subgroups

Subgroup		High dose N	High dose %	Low dose N	Low dose %	RR	LCL	UCL
GENDER	Female	317	39.75	331	38.37	1.04	0.85	1.26
	Male	1251	43.17	1265	46.64	0.93	0.85	1.01
RACE	Afro-Car	99	39.39	105	40.95	0.96	0.69	1.35
	Asian	52	42.31	40	37.50	1.13	0.68	1.88
	Caucasian	1417	42.70	1451	45.42	0.94	0.87	1.02
AGE	< 70	1055	36.21	1121	41.57	0.87	0.78	0.97
	70+	513	55.36	475	52.84	1.05	0.93	1.18
NYHA	II	262	34.35	231	41.99	0.82	0.65	1.03
	III	1194	42.55	1252	43.69	0.97	0.89	1.07
	IV	112	60.71	113	64.60	0.94	0.77	1.15
LVEF	< median	766	47.52	784	49.62	0.96	0.86	1.06
	>=median	800	37.63	810	40.37	0.93	0.82	1.05
Use of ACEi	No	178	39.33	176	38.64	1.02	0.78	1.32
	Yes	1390	42.88	1420	45.70	0.94	0.86	1.02
Use of Anti-arrhythmics	No	1427	42.19	1431	45.14	0.93	0.86	1.02
	Yes	141	45.39	165	43.03	1.05	0.82	1.36
Use of Anti-hypertensives	No	1565	42.49	1588	44.84	0.95	0.88	1.03
	Yes	3	33.33	8	62.50	0.53	0.10	2.88
Use of Aspirin	No	934	43.04	952	45.90	0.94	0.85	1.04
	Yes	634	41.64	644	43.48	0.96	0.84	1.09
Use of beta blockers	No	1413	43.38	1398	46.64	0.93	0.86	1.01
	Yes	155	34.19	198	32.83	1.04	0.78	1.40
Use of Calcium channel blockers	No	1385	41.95	1410	44.68	0.94	0.86	1.02
	Yes	183	46.45	186	46.77	0.99	0.80	1.24
Use of NSAID	No	1548	42.25	1568	45.09	0.94	0.87	1.01
	Yes	20	60.00	28	35.71	1.68	0.91	3.10
Use of positive inotrope	No	1567	42.44	1592	44.79	0.95	0.88	1.03
	Yes	1	100.00	4	100.00	1.00	1.00	1.00

RR: relative risk
LCL: lower limit of 95% confidence interval
UCL: upper limit of 95% confidence interval

Table A.2 All cause mortality and all cause hospitalizations by Subgroups

Subgroup		High dose N	High dose %	Low dose N	Low dose %	RR	LCL	UCL
GENDER	Female	317	77.60	331	82.78	0.94	0.87	1.01
	Male	1251	80.26	1265	84.11	0.95	0.92	0.99
RACE	Afro-Car	99	83.84	105	77.14	1.09	0.95	1.24
	Asian	52	78.85	40	90.00	0.88	0.74	1.04
	Caucasian	1417	79.46	1451	84.15	0.94	0.91	0.98
AGE	< 70	1055	77.16	1121	81.71	0.94	0.90	0.99
	70+	513	84.99	475	88.84	0.96	0.91	1.00
NYHA	II	262	75.95	231	85.28	0.89	0.82	0.97
	III	1194	79.65	1252	83.07	0.96	0.92	1.00
	IV	112	89.29	113	89.38	1.00	0.91	1.09
LVEF	< median	766	80.16	784	85.71	0.94	0.89	0.98
	>=median	800	79.25	810	82.10	0.97	0.92	1.01
Use of ACEi	No	178	75.28	176	79.55	0.95	0.85	1.06
	Yes	1390	80.29	1420	84.37	0.95	0.92	0.98
Use of Anti-arrhythmics	No	1427	79.75	1431	83.79	0.95	0.92	0.99
	Yes	141	79.43	165	84.24	0.94	0.85	1.05
Use of Anti-hypertensives	No	1565	79.68	1588	83.82	0.95	0.92	0.98
	Yes	3	100.00	8	87.50	1.14	0.88	1.49
Use of Aspirin	No	934	78.16	952	83.82	0.93	0.89	0.97
	Yes	634	82.02	644	83.85	0.98	0.93	1.03
Use of beta blockers	No	1413	79.97	1398	83.98	0.95	0.92	0.99
	Yes	155	77.42	198	82.83	0.93	0.84	1.04
Use of Calcium channel blockers	No	1385	78.77	1410	84.04	0.94	0.90	0.97
	Yes	183	86.89	186	82.26	1.06	0.97	1.15
Use of NSAID	No	1548	79.65	1568	83.80	0.95	0.92	0.98
	Yes	20	85.00	28	85.71	0.99	0.78	1.26
Use of positive inotrope	No	1567	79.71	1592	83.79	0.95	0.92	0.98
	Yes	1	100.00	4	100.00	1.00	1.00	1.00

RR: relative risk
LCL: lower limit of 95% confidence interval
UCL: upper limit of 95% confidence interval

Related Publications

TI: Results of the ATLAS study. High or low doses of ACE inhibitors for heart failure?
AU: Hobbs-RE
SO: Cleve-Clin-J-Med. 1998 Nov-Dec; 65(10): 539-42
ISSN: 0891-1150
LA: ENGLISH

TI: ATLAS: high dose lisinopril is superior to low dose in heart failure [editorial]
AU: Jackson-G
SO: Int-J-Clin-Pract. 1998 Apr-May; 52(3): 139
ISSN: 1368-5031
LA: ENGLISH

TI: Regional differences in the characteristics and treatment of patients participating in an international heart failure trial. The Assessment of Treatment with Lisinopril and Survival (ATLAS) Trial Investigators.
AU: Massie-BM; Cleland-JG; Armstrong-PW; Packer-M; Poole-Wilson-PA; Lars-R
SO: J-Card-Fail. 1998 Mar; 4(1): 3-8
ISSN: 1071-9164
LA: ENGLISH

TI: ATLAS shows global undertreatment of heart failure [news]
AU: Husten-L
SO: Lancet. 1998 Apr 4; 351(9108): 1035
ISSN: 0140-6736
LA: ENGLISH

TI: Do angiotensin-converting enzyme inhibitors prolong life in patients with heart failure treated in clinical practice? [editorial]
AU: Packer-M
SO: J-Am-Coll-Cardiol. 1996 Nov 1; 28(5): 1323-7
ISSN: 0735-1097
LA: ENGLISH

TI: [Lisinopril in the treatment of heart insufficiency]
AU: Barcina-Sanchez-C; Martin-Cortes-M; Fernandez-Fernandez-A
SO: An-Med-Interna. 1995 May; 12(5): 246-53
ISSN: 0212-7199
LA: SPANISH; NON-ENGLISH

TI: [The ATLAS study (Assessment of Treatment with Lisinopril and Survival); justification and objectives]
AU: Komajda-M; Wimart-MC; Thibout-E
SO: Arch-Mal-Coeur-Vaiss. 1994 Jun; 87 Spec No 2: 45-50
ISSN: 0003-9683
LA: FRENCH; NON-ENGLISH

481

FEB 3 1999

MEMORANDUM

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

Date: 02/03/99

From: Shaw T. Chen, M.D., Ph.D., Medical Group Leader, HFD-110
Through: Director, Division of Cardiorenal Drug Products, HFD-110
To: NDA-19777 File -S037

SUBJECT: Review of NDA-19777 S-037 in Taiwan

I am applying for permission to carry out a joint medical-statistical review of the above application while stationed in Taipei, Taiwan as an FDA advisor to Taiwan's Center for Drug Evaluation (CDE) (see attached agreement between FDA and Taiwan's Department of Health).

I understand that I will need to maintain the same standards of conduct with regard to confidentiality as if I were at my official duty station in Rockville, Maryland. It will be my responsibility to protect the NDA-related documents sent to me in Taiwan.

From my alternate site in Taiwan, I will use telephone, fax and e-mail to discuss the application with my colleagues at FDA and the sponsor. I will make sure these channels of communication are reasonably secure.

The sponsor has granted permission for the off-site review (Jan. 20, 1999 correspondence).

cc: NDA 19-777 /S-037
HFD-110
HFD-110 / KBongiovanni

CENTER FOR DRUG EVALUATION AND RESEARCH

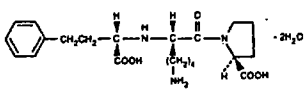
APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 19-777/S-037

Chemistry Review(s)

MAR 29 1999

CHEMIST'S REVIEW	1. ORGANIZATION HFD-110	2. NDA Number 19-777
3. Name and Address of Applicant (City & State) Zeneca Pharmaceuticals Wilmington, DE 19850-5437		4. Supplement(s) Number(s) Date(s) S-037 29 Jan 99
5. Drug Name Zestril	6. Nonproprietary Name Lisinopril	7. Amendments & Other (reports, etc) - Dates NC 29 Jan 99
8. Supplement Provides For: Use of Zestril as adjunctive therapy in the management of heart failure patients not responding adequately to diuretics and digitalis.		
9. Pharmacological Category Antihypertensive	10. How Dispensed [X] 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  1-[N^2-[(S)-1-Carboxy-3-phenylpropyl]-L-lysyl]-L-proline dihydrate		15. Records/Reports Current [X] Yes [ ] No Reviewed [X] Yes [ ] No

16. Comments:

This submission is an efficacy supplement which provides for use of Zestril in treatment of congestive heart failure.

The amendment provides patent information. The proposed new indication is claimed in US 4,374,829. This information was also included in the original submission.

No changes are proposed in manufacture and control of either the drug substance or drug product.

No changes have been made in the DESCRIPTION and HOW SUPPLIED sections of the Package Insert, and no changes are proposed for the container labels.

The firm requests a categorical exclusion for an environmental assessment for this supplement in accordance with 21 CFR 25.31(a) and (b). The request is acceptable.

17. Conclusions and Recommendations:

There are no CMC issues which should impede approval of this supplement.

18. REVIEWER

Name James H. Short Signature James H. Short Date Completed 9 Feb 99

Distribution: [X] Original Jacket [ ] Reviewer [ ] Division File [ ] CSO

jhs/2/9/99/N19-777.S37

K. Srinivasan 3-29-99

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 19777/S-037

Clinical Pharmacology and Biopharmaceutics Review

JUL 2 6 1999

Clinical Pharmacology/Biopharmaceutics Review

NDA: 19-777
Serial #: S-037; SEI-037 (BB)
Compound #: Zeneca ZD1262 (Zestril, lisinopril) 30mg tablets
Zeneca Pharmaceuticals
Submission Date: June 14, 1999; July 15, 1999

Reviewer: Thomas A. Parmelee, Pharm.D.

Type of Submission: Clinical Pharmacology/Biopharmaceutics Consult- A Bioequivalence Study for a new Tablet Strength-Trial 1262IL/0027

BACKGROUND

Lisinopril (Zestril) is an inhibitor of the angiotensin converting enzyme (ACE) system. By preventing the formation of the potent vasoconstrictor angiotensin II from angiotensin I, lisinopril and other ACE inhibitors are effective anti-hypertensive drugs. ACE inhibitors have also been shown to be effective treatment for congestive heart failure (CHF). By reducing cardiac filling pressure and volume, these agents have improved the survival of patients with CHF in large outcome trials. Nonetheless, ACE inhibitors are often under-prescribed in CHF patients due to possible misunderstanding of their benefits, or concerns over the safety of higher doses in this patient population.

A large multi-national, double-blind, randomized, parallel-group controlled trial was designed to evaluate the efficacy and safety of high dose (32.5mg or 35mg) and low dose (2.5mg or 5.0mg) treatment of CHF patients with lisinopril. This trial was named: "Assessment of Treatment with Lisinopril and Survival (ATLAS). The objective of this large clinical trial was to compare the effects of 30mg lisinopril or placebo on the mortality and morbidity of CHF patients receiving background low dose lisinopril (2.5mg or 5.0 mg). The results showed that patients receiving the high dose lisinopril had a significant reduction in all-cause mortality and hospitalization compared with the patients receiving lower doses.

Zeneca has produced 30mg lisinopril tablets for convenience and compliance enhancement. Current formulations of lisinopril include: 5, 10, and 20mg tablets. The purpose of the present submission was to compare the pharmacokinetic profiles of three 10mg lisinopril tablets vs. one newly manufactured 30mg tablet in healthy male and female subjects. The study summary is attached to this review. A copy of the manufacturing formula for the new 30mg tablet strength is also attached to the present review.

ASSAY

Lisinopril is determined in human serum and urine using RIA with I-125 labeled tracer and anti-lisinopril serum.

1) Serum QC samples-lisinopril:

Nominal Conc. (ng/mL)	N	Mean Conc. (ng/mL)	SD	CV%	Accuracy (%)
0.5	46	0.5	± 0.1	16.7	100.0
1.5	46	1.4	± 0.2	12.3	93.3
28	46	29.5	± 8.5	28.9	106.4

2) Urine QC samples-lisinopril:

Nominal Conc. (ng/ mL)	N	Mean Conc. (ng/mL)	SD	CV%	Accuracy (%)
0.5	18	0.5	± 0.2	31.2	100.0
1.5	20	1.4	± 0.4	24.5	93.3
28	18	36	± 15.4	42.8	128.6

RESULTS

Thirty-five of the 36 subjects received both treatment arms of the study. One subject was withdrawn after receiving the 3 x 10mg lisinopril treatment in period 1 due to a viral infection. This was not considered drug-related.

Table 1 below shows the mean pharmacokinetic results for both treatments as well as the ratios and 90% confidence intervals of the ratios:

Table 1: Primary analysis of pharmacokinetic parameters for 1 x 30mg lisinopril and 3 x 10mg lisinopril tablets

Parameter	1x30mg		3x10mg		ratio of glsmeans*	90% CI
	N	glsmean	N	glsmean		
-AUC(0-t) (ng.h/mL)	35	1600.51	36	1589.37	1.01	0.92 to 1.10
-Cmax (ng/mL)	35	124.68	36	126.06	0.99	0.88 to 1.11
-% of dose in urine	31	21.27	36	21.59	0.99	0.88 to 1.10
-Renal CL (mL/min)	31	68.55	36	67.91	1.01	0.94 to 1.08

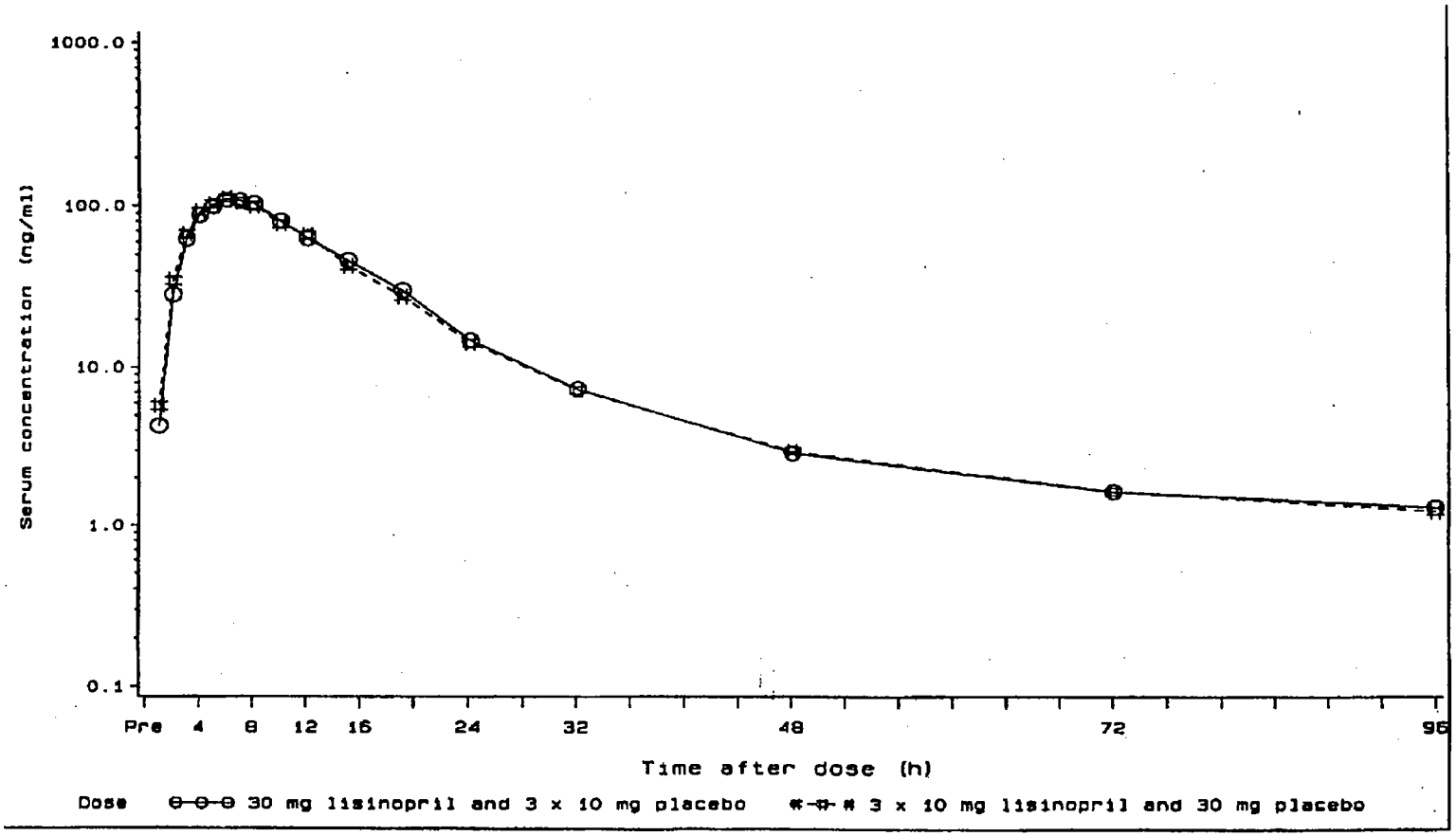
* Ratio expressed as 30mg lisinopril/3 x 10mg lisinopril
glsmean = Least squares geometric mean

Median Tmax was 6 hours for both formulations in this study. The range for the 30mg lisinopril (plus 3 x 10mg placebo) was 4.0-8.0 hours while the range for the 3 x 10mg lisinopril (plus 30mg placebo) was 2.1-12.5 hours. The sponsor did not perform a statistical analysis of Tmax for this study.

Figure 1 shows the geometric mean serum concentration vs. time for both the 1 x 30mg tablet and 3 x 10mg tablets:

Appears This Way
On Original

Figure 1 Geometric mean serum concentrations for 1 x 30 mg tablet and 3 x 10 mg tablets of lisinopril



RESULTS

1) The newly manufactured 30mg lisinopril tablet appears to be bioequivalent to 3 x 10mg lisinopril tablets that were used in the ATLAS efficacy trial based on the 90% confidence intervals for the PK parameters AUC (0-t) and Cmax of the ratios between treatments. The sponsor also performed statistical analyses on the percentage of drug excreted in urine and renal clearance for both treatment groups. The 90% confidence intervals for all ratio comparisons were within the 80-125% range generally required to demonstrate bioequivalence.

2) The sponsor was contacted on July 8 and July 13 1999 via Robert Orzolek, and was requested to submit individual patient data of AUC (0-inf) for both study treatments, the % extrapolation from AUC (0-t) to AUC (0-inf) for both study treatments, and 90% confidence intervals for the treatment ratios of AUC (0-inf).

3) The sponsor submitted the requested information via telefax as seen copied to this review. Table 2 of the telefax data shows the 90% CI's for the ratio of least square geometric means for the AUC (0-inf) to be 0.93 to 1.11. The % extrapolation of AUC (t-inf) to AUC (0-inf) is provided for each study subject. The mean % extrapolation from either treatment was less than 10%.

DISSOLUTION

The dissolution profile for the new 30mg tablet was compared to the dissolution profile for 3 x 10mg lisinopril approved tablets. A copy of the comparison is attached to this review. The sponsor calculated a similarity factor (f2) to be 75.75. Ideally, individual unit testing is recommended. The sponsor should have tested an individual 30mg tablet, and then performed individual unit testing of the 10mg tablet. Based on the % dissolved, a similarity factor (f2) can be calculated for the comparison between these individual dissolution profiles. Since the product is rapidly dissolving, however, the comparison made by the sponsor is acceptable.

COMMENTS (to the clinical division and sponsor)

1) This bioequivalence study is acceptable to the Office of Clinical Pharmacology and Biopharmaceutics. The new 30mg lisinopril tablet is bioequivalent to 3 x 10mg lisinopril tablets that were used in pivotal clinical efficacy studies. This conclusion is based on the 90% confidence intervals for the ratios of AUC (0-t), AUC (0-inf), and Cmax between treatments. Also, both treatments had a median Tmax value of 6 hours. All 90% confidence intervals were within the 0.80 to 1.25 range generally required to show bioequivalence.

2) The sponsor is requested to adopt and apply the currently established dissolution method and specification, used for other strengths of lisinopril tablets, to the new 30mg tablet:

Method: Apparatus II (paddle)
Speed: 50 rpm
Medium: 900mL 0.1 N hydrochloric acid
Specs: Q not less than 80% in 30 minutes

RECOMMENDATIONS

From a bioequivalency standpoint, the 30mg tablet is approved. The sponsor is requested to adopt the currently approved dissolution method and specification for the new 30mg tablet. Please convey this recommendation and above comments 1-2 to the sponsor.

Thomas A. Parmelee, Pharm.D. 7/26/99

RD/FT by R. Baweja, Ph.D. R. Baweja 7/26/99

CC: NDA 19-777, HFD-110, HFD-860 (Mehta, Baweja, Parmelee), CDER document room: Attn. BIOPHARM- CDR

SUMMARY

ZENECA PHARMACEUTICALS

FINISHED PRODUCT: ZESTRIL™

ACTIVE INGREDIENT: Lisinopril

Trial title (number): A Phase I, single-blind, randomised, two-way crossover trial to assess whether a 30 mg lisinopril tablet is bioequivalent to three 10 mg lisinopril tablets when given to healthy male and female volunteers. (1262IL/0027)

Clinical phase: I

First volunteer entered: 2 March 1998
Last volunteer completed: 16 April 1998
Zeneca approval date: 15 October 1998

Principal investigator and location: Clinical Pharmacology Unit, Zeneca Pharmaceuticals, Mereside, Alderley Park, Macclesfield, Cheshire, UK, SK10 4TG.

Publications: None at the time of writing this report.

OBJECTIVES

The primary objective was to compare the pharmacokinetics [AUC(0–t)] of a 30 mg lisinopril tablet with the pharmacokinetics of three 10 mg tablets when given to healthy male and female volunteers.

The secondary objectives were to compare:

- the maximum serum concentrations (C_{max})
- times to maximum serum concentration (t_{max})
- amounts of drug excreted in the urine (Ae_{∞})
- apparent renal clearance (Ae_{∞}/AUC)

In addition, the safety of all volunteers was to be ensured by clinical monitoring.

METHODS

Design: A single-blind, randomised, two-way crossover, single-centre trial in healthy male and female volunteers. Following an overnight fast, 2 single 30 mg doses (1 x 30 mg and 3 x 10 mg) of lisinopril were given to volunteers. Doses were separated by a 3-week washout period.
Population: A total of 36 healthy male and female volunteers were required to enter the trial. Key inclusion criteria: Male or female, aged between 18 and 55 years; normal clinical examination, including medical history, resting electrocardiogram (ECG) and 24-hour continuous ambulatory ECG; if female, a negative pregnancy test performed at the pre-trial medical and before pre-dose assessments on each trial day.
Key exclusion criteria: Use of any medication or therapy (hormone replacement therapy [HRT] and combined oral contraceptive pills [OCPs] were permitted for females); receipt of another new chemical entity in the 6 months before this trial; participation in another trial within 3 months before the start of this trial, apart from non-invasive methodology trials in which no drugs were given; any acute illness within 2 weeks before the start of the trial; any clinically significant abnormalities in clinical chemistry, haematology or urinalysis results; definite or suspected personal history or family history of adverse drug reactions, or hypersensitivity to drugs with a similar chemical structure or mechanism of action to lisinopril (eg, ACE inhibitors); history or presence of gastrointestinal, hepatic or renal disease or other condition known to interfere with absorption, distribution, metabolism or excretion of drugs; history of hereditary or idiopathic oedema; excessive intake of alcohol; treatment in the previous 3 months with any drug known to have a well-defined potential for hepatotoxicity (eg, halothane); supine diastolic blood pressure above 90 mmHg; pregnancy, breast feeding or not using an effective method of contraception; females taking diuretics for the treatment of cyclical oedema.
Dosage: Volunteers received both of the following dose combinations in a randomised order:

- 1 x 30 mg lisinopril tablet plus 3 x placebo to 10 mg lisinopril tablets
- 3 x 10 mg lisinopril tablets plus 1 x placebo to 30 mg lisinopril tablet

Pharmacokinetics: Blood and urine samples were taken for assessment of the following parameters: area under the plasma concentration-time curve from 0 to time t (AUC(0-t)), C_{max}, t_{max}, Ae_{∞}, Ae_{∞}/AUC.
Safety: Safety was assessed by recording adverse events, clinical laboratory data, subjective symptomatology, medical examinations, ECG, blood pressure and pulse rate.

RESULTS

Demography: A total of 36 Caucasian volunteers entered this trial; 18 male and 18 female. Thirty five volunteers completed the trial. The average age of the female volunteers was 35.9 years (range 24 to 51 years) and of the male volunteers was 35.5 years (range 22 to 55 years).
Pharmacokinetics: The ratios of the geometric means of all the parameters statistically analysed were close to unity and the 90% confidence intervals were within the protocolled limits of 0.8 to 1.25. The median t_{max} for both tablet formulations was 6 hours.

Table I Primary analysis of pharmacokinetic parameters for 30 mg lisinopril tablet and 3 x 10 mg lisinopril tablets

Parameter	1 x 30 mg lisinopril		3 x 10 mg lisinopril		Ratio of glsmeans[a]	90% confidence interval
	n	glsmean	n	glsmean		
AUC(0-t) (ng.h/ml)	35	1600.51	36	1589.37	1.01	0.92 to 1.10
C_{max} (ng/ml)	35	124.68	36	126.06	0.99	0.88 to 1.11
% of dose excreted in urine	31	21.27	36	21.59	0.99	0.88 to 1.10
Renal clearance (ml/min)	31	68.55	36	67.91	1.01	0.94 to 1.08

[a] Ratio expressed as 30 mg lisinopril /3 x 10 mg lisinopril
AUC Area under the curve.
C_{max} Maximum plasma concentration.
glsmean Least squares geometric mean.

These results were validated by a subsidiary analysis performed after subtracting the pre-dose concentration and 96 times the pre-dose concentration from the C_{max} and AUC(0-t) values.
Safety: Twenty two volunteers (63%) experienced a total of 41 adverse events following exposure to the 30 mg tablet formulation and 25 volunteers (69%) experienced a total of 55 adverse events following exposure to 3 of the 10 mg tablet formulation. None of the adverse events was serious and only one, a viral infection, led to withdrawal from the trial.

OVERALL CONCLUSIONS

This trial has demonstrated that the 30 mg lisinopril tablet and 3 x 10 mg lisinopril tablets are bioequivalent, based on the statistical analyses of AUC(0-t), C_{max}, percentage of drug excreted in urine and renal clearance. The median t_{max} was also identical for both formulations.
There were no serious adverse events in this trial and both formulations were equally well tolerated.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

19-777/S-037

Administrative/Correspondence Reviews

Zeneca Pharmaceuticals,
A Business Unit of Zeneca Inc.
Drug Regulatory Affairs Department
Wilmington, DE 19850-5437

ZESTRIL® (lisinopril) Tablets
NDA 19-777

Pursuant to Section 505 of the Federal Food, Drug and Cosmetic Act, the attached information following below is made of record.

A. PATENT INFORMATION ON ANY PATENT WHICH CLAIMS THE DRUG OR A METHOD OF USING THE DRUG

CERTIFICATION

Pursuant to 21 CFR section 314.53(d)(2)(ii), Zeneca Ltd., through its Agent Zeneca Pharmaceuticals, a Business Unit of Zeneca Inc. (hereinafter for this document, "Zeneca Pharmaceuticals") certifies that U.S. Patent No.4,374,829, information relative to which has previously been submitted, claims the change in ZESTRIL® (lisinopril) Tablets which is the subject of this supplemental new drug application.

Richard A. Elder

RICHARD A. ELDER
CHIEF IP COUNSEL
PHARMACEUTICALS

EXCLUSIVITY SUMMARY FOR NDA # 19-777 SUPPL #_037_____

Trade Name Zestril Generic Name Lisinopril

Applicant Name Zeneca Pharmaceuticals HFD # 110

Approval Date If Known _____

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?
YES /___/ NO /_X__/

b) Is it an effectiveness supplement?

YES /_X__/ NO /___/

If yes, what type? (SE1, SE2, etc.) SE1

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /_X__/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

Form OGD-011347 Revised 10/13/98
cc: Original NDA Division File HFD-93 Mary Ann Holovac

d) Did the applicant request exclusivity?

YES /_X__/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request? 3 Years

e) Has pediatric exclusivity been granted for this Active Moiety? NO

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO-please indicate as such)

YES /___/ NO /_X__/

If yes, NDA #_____. Drug Name _____.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X__/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_X__/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_X__/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /_X_/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /_X__/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_X__/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

1. ATLAS Trial
2. Bioequivalence Study (10mg vs 30mg lisinopril tablets) Trial 1262L/0027

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 ATLAS Trial YES /___/ NO /_X__/

Investigation #2 Bio Study-Trial 1262L/0027 YES /___/ NO /_X__/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 ATLAS Trial YES /___/ NO /_X__/

Investigation #2 Bio Study-Trial 1262L/0027 YES /___/ NO /_X_/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

ATLAS Trial
Bio Study-Trial 1262L/0027

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 ATLAS Trial

IND# 33,691 YES /_X__/ NO /___/ Explain: _____

Investigation #2 Bio Study-Trial 1262L/0027

IND # 33,691 YES /_X__/ NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_X__/

If yes, explain: _____

_____

Signature Zelda McDonald Date 11/10/99
Title: Regulatory Health Project Manager

Signature Ray Lipicky Date 11/25/99
Division Director

cc: Original NDA Division File HFD-93 Mary Ann Holovac

B. EXCLUSIVITY INFORMATION

1. Exclusivity Claim

Zeneca Pharmaceuticals claims an exclusivity period of three years for the change in ZESTRIL® (lisinopril) Tablets presented in this supplemental new drug application.

2. Authority for Exclusivity Claim

Exclusivity for the change in ZESTRIL® (lisinopril) Tablets presented in this supplemental new drug application is being claimed pursuant to 21 CFR Section 314.108(b)(5).

3. Information Demonstrating this Supplemental Application Contains New Clinical Investigations Conducted or Sponsored by the Applicant that are Essential to the Approval of this Supplemental New Drug Application.

a. Certification of New Clinical Investigations

Zeneca Pharmaceuticals certifies that to the best of Zeneca Pharmaceuticals' knowledge, each of the clinical investigations included in this supplemental new drug application meets the definition of "new clinical investigation" set forth in 21 CFR Section 314.108(a).

HOWARD G. HUTCHINSON, M.D.
SENIOR MEDICAL DIRECTOR

b. Essential to Approval

(i) Literature Search

Attached as Exhibit A is a list of all published studies and publicly available reports of clinical investigations known to Zeneca Pharmaceuticals through a literature search that are relevant to the conditions for which Zeneca Pharmaceuticals is seeking approval.

c. Conducted or Sponsored by the Applicant.

Zeneca Pharmaceuticals, A Business Unit of Zeneca Inc., the agent and a wholly-owned subsidiary of Zeneca Ltd., is the sponsor named in form FDA-1571 for IND 33,961 under which the new clinical investigation essential to the approval of this supplemental new drug application was conducted. We believe this fact is sufficient under 21 CFR 314.50(j)(4)(iii) to establish that the clinical investigations were conducted or sponsored by the Applicant.

(ii) Certification

Zeneca Pharmaceuticals certifies that Zeneca Pharmaceuticals has thoroughly searched the scientific literature and, to the best of Zeneca Pharmaceuticals' knowledge, the list of relevant published studies and/or publicly available reports is complete and accurate, and in Zeneca Pharmaceuticals' opinion, such published studies and/or publicly available reports do not provide a sufficient basis for the approval of the conditions for which Zeneca Pharmaceuticals is seeking approval without reference to the new clinical investigation(s) in this supplemental new drug application.

Howard G. Hutchinson

HOWARD G. HUTCHINSON, M.D.
SENIOR MEDICAL DIRECTOR

(iii) Explanation

The published studies listed in Exhibit A do not provide sufficient basis for the approval of high doses of ZESTRIL® (lisinopril) to reduce the risk of the combined outcomes of mortality and hospitalization in patients with congestive heart failure without reference to the new clinical investigation in this supplemental new drug application. The reasons are as follows:

First, the studies cited in Exhibit A used ACE inhibitors other than lisinopril. Second, these trials were not appropriately designed to test the hypothesis that higher doses of ACE inhibitors provide a cardiovascular outcome benefit in patients with congestive heart failure.

The ATLAS trial results provide the only available information regarding the benefits afforded by higher doses of lisinopril, and data from this trial provide the basis for the current sNDA submission.

The NETWORK Investigators. Clinical outcome with enalapril in symptomatic chronic heart failure; a dose comparison. European Heart Journal 1998;19:481-489.

Van Veldhuisen DJ, Genth-Zoth S, Brouwer J, Boomsma F, Netzer T, Man In 'T Veld AJ, Pinto YM, Lie KI Crijns HJGM. High-versus low-dose ACE inhibition in chronic heart failure. A double-blind, placebo-controlled study of imidapril. J Am Coll Cardiol 1998;32:1811-1818.

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at time of the last action.

NDA/BLA # 19777 Supplement # 037 Circle one: (SE1) SE2 SE3 SE4 SE5 SE6

HFD-110 Trade and generic names/dosage form: Zestril (lisinopril) Tablets Action: AP AE NA

Applicant Zeneca Pharmaceuticals Therapeutic Class 6S

Indication(s) previously approved Hypertension, Heart failure, Acute myocardial Infarction
Pediatric information in labeling of approved indication(s) is adequate ___ inadequate ___
Indication proposed in this application NA

FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION.

IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS? ✓Yes (Continue with questions) ___No (Sign and return the form)

IN WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED? (Check all that apply)
___Neonates (Birth-1month) ✓Infants (1month-2yrs) ✓Children (2-12yrs) ✓Adolecents(12-16yrs)

___1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

___2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

___3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

- ___a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.
- ___b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.
- ___c. The applicant has committed to doing such studies as will be required.
  - ___ (1) Studies are ongoing,
  - ___ (2) Protocols were submitted and approved.
  - ___ (3) Protocols were submitted and are under review.
  - ___ (4) If no protocol has been submitted, attach memo describing status of discussions.
- ___d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

✓4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

___5. **If none of the above apply,** attach an explanation, as necessary.

ARE THERE ANY PEDIATRIC PHASE 4 COMMITMENTS IN THE ACTION LETTER? ___ Yes ✓No
ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

This page was completed based on information from medical officer (team leader) (e.g., medical review, medical officer, team leader)

Zelda McDonald, RHPM
Signature of Preparer and Title

Date 10/29/99

cc: Orig (NDA)/BLA # 19-777
HFD-110 /Div File
NDA/BLA Action Package
HFD-~~999~~/ ~~KRoberts~~ T Crescenzi

(revised 10/20/97)

FOR QUESTIONS ON COMPLETING THIS FORM, CONTACT KHYATI ROBERTS, HFD-6 (ROBERTSK)

Pediatric Memo

1. Heart failure is rare in children.
2. A Pediatric Written Request (Exclusivity) has been sent to the Sponsor for hypertension. Information on use in children with heart failure can be obtained from the hypertension database should the sponsor submit one.

Zeneca ZD1262 (lisinopril, ZESTRIL™)

DEBARMENT CERTIFICATION

For further information regarding this section, please contact:

Robert J. Orzolek
Assistant Manager, Marketed Products Group
(302) 886-4550
Zeneca Pharmaceuticals
A Business Unit of Zeneca Inc.
1800 Concord Pike
PO Box 15437
Wilmington, DE 19850-5437

ZENECA
Pharmaceuticals Group
ZENECA Pharmaceuticals / Stuart Pharmaceuticals
Business Units of ZENECA Inc

1800 Concord Pike
Wilmington
Delaware 19897 USA

Telephone (302) 886-2132
Fax (302) 886-2822

William J. Kennedy, Ph.D.
Vice President
Drug Regulatory Affairs Department

January 20, 1999

Re ZESTRIL® (lisinopril)
Supplemental NDA (ATLAS Trial)
NDA 19-777

In response to the requirements of the Generic Drug Enforcement Act of 1992, I hereby certify on behalf of Zeneca Pharmaceuticals, a Business Unit of Zeneca Inc , that we did not and will not use in connection with this application, the services of any person in any capacity debarred under section 306 (a) or (b).

Sincerely,

William J. Kennedy, Ph.D.

WJK/DAG/car

orig.

FEB 7 2000

RHPM Review of Final Printed Labeling
NDA

Date of Submission:	December 30, 1999
Date of Review:	January 18, 2000
Applicant Name:	Zeneca Pharmaceuticals
Product Name:	Zestril (lisinopril) 2.5, 5, 10, 20, 30, and 40 mg Tablets

Evaluation:

This submission provides for final printed labeling (FPL) in accordance with our approvable letter dated December 2, 1999. The following change in FPL was noted: Under Dosage and Administration/Heart Failure, the word "daily" was inserted by the sponsor between "single" and "dose" in the second paragraph. Dr. Shaw Chen stated on January 14, 2000 that this change is acceptable.

An approval letter should issue for this application.

Sandra Birdsong 2/7/00

Sandra Birdsong, RHPM

Cc: orig. NDA
HFD-110
HFD-110/SBirdsong
HFD-110/ABlount

Cc: orig.NDA
HFD-110
HFD-110/Birdsong
HFD-110/Blount
HF-2

OFFICES OF DRUG EVALUATION
ORIGINAL NDA/NDA EFFICACY SUPPLEMENT
ACTION PACKAGE CHECKLIST

NDA#19-777/S037 Drug **Zestril (lisinopril)**

Applicant **Zeneca Pharmaceuticals** Chem/Ther/Other Types: **6S**

PM: **Sandy Birdsong** Phone: **301-594-5312** **HFD-110**

USER FEE GOAL DATE: **December 2, 1999** DATE CHECKLIST COMPLETED: **January 24, 2000**

		Check or Comment
1.	ACTION LETTER with supervisory signatures	**AP**
	Are there any Phase 4 commitments?	**No**
2.	Have all disciplines completed their reviews?	**Yes**
	If no, what reviews are still in draft?	
3.	LABELING (package insert and carton and container labels).	**Final**
	(If final or revised draft, include copy of previous version with ODE's comments and state where in action package the Division's review is located. If Rx-to-OTC switch, include current Rx Package insert and HFD-312 and HFD-560 reviews of OTC labeling.)	
4.	Package inserts of the last 3 drugs approved that are of similar pharmacologic class.	X
5.	CLINICAL INVESTIGATOR FINANCIAL DISCLOSURE	X
6.	PATENT INFORMATION	X
7.	EXCLUSIVITY CHECKLIST	X
8.	PEDIATRIC PAGE (all NDAs)	X
9.	DEBARMENT CERTIFICATION (Copy of applicant's certification [all NDAs submitted after 1992]).	X
10.	Statement on status of DSI's AUDIT OF MAJOR CLINICAL STUDIES	X
	If AE or AP ltr, explain if not satisfactorily completed. Attach a COMIS printout of DSI status. If no audits were requested, include a memo explaining why.	
11.	REVIEWS [If more than 1 review for any 1 discipline, separate reviews with a sheet of colored paper. Any conflicts between reviews must have resolution documented.]:	
	DIVISION DIRECTOR'S MEMO	
	GROUP LEADER'S MEMO	
	MEDICAL/STATISTICAL REVIEW	**X**
	SAFETY UPDATE REVIEW	
	BIOPHARMACEUTICS REVIEW	X
	PHARMACOLOGY REVIEW (include pertinent IND reviews)	
	Statistical Review of Carcinogenicity Study(ies)	
	CAC Report/Minutes	
	CHEMISTRY REVIEW	
	Labeling and Nomenclature Committee Review Memorandum	
	Date EER completed (attach signed form or CIRTS printout)	OK No
	FUR needed FUR requested	
	Have methods been validated?	Yes (attach) No
	Environmental Assessment Exclusion	
	If no exclusion, Review/FONSI	
	MICROBIOLOGY REVIEW	
	What is the status of the monograph?	
12.	CORRESPONDENCE and FAXes	X
13.	13. Minutes of Meetings including Telecons and Memoranda	
	Date of End-of-Phase 2 Meeting	
	Date of pre-IND Meeting	
14.	ADVISORY COMMITTEE MEETING MINUTES	Minutes NA Info Alert
	or, if not available, 48-hour Info Alert or pertinent section of transcript	Transcript No Mtg
15.	FEDERAL REGISTER NOTICES; OTC or DESI DOCUMENTS	NA
16.	If approval letter, has ADVERTISING MATERIAL been reviewed?	No
	If no and this is an AP with draft labeling letter, has advertising material already been requested?	Yes No **No, included in AP ltr**
17.	INTEGRATED SUMMARY OF EFFECTIVENESS (from NDA)	**NA, only one study**
18.	INTEGRATED SUMMARY OF SAFETY (from NDA)	**NA, only one study**

DEC - 8 1999

ZENECA
Pharmaceuticals
A Business Unit of Zeneca Inc.

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

SENT VIA FACSIMILE

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, Room No. 5039
1451 Rockville Pike
Rockville, MD 20852

Dear Dr. Lipicky:

Re: ZESTRIL® (lisinopril) Tablets
NDA 19-777/S-037
Teleconference - Proposed Labeling

For your consideration prior to our teleconference on Thursday, December 9, 1999, at 10:00 AM, we are proposing for discussion the following language for the Clinical Pharmacology section of the labeling for ZESTRIL® (lisinopril) Tablets as an alternative to the labeling provided by the Agency in its December 2, 1999 approvable letter for the above referenced supplemental New Drug Application (sNDA)

> 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.

The proposed labeling language was compiled from the language that was stricken from the Clinical Pharmacology section of the labeling document forwarded to Zeneca by the Agency. It appears to Zeneca that the language stricken from the document was written by the FDA during the review of the application. Zeneca is requesting the FDA's view as to whether, outside of taking this matter to an Advisory Committee, the Agency would be amenable to considering a labeling revision to the Clinical Pharmacology section such as that provided above.

The FDA will initiate the teleconference by contacting Zeneca Pharmaceuticals at (302) 886-4228. Participating in the teleconference for Zeneca Pharmaceuticals will be Howard G. Hutchinson, MD, Senior Medical Director; B. Christine Clark, Ph.D., Biostatistics Product Team Leader; Kevin McKenna, Ph.D., Executive Director, CNS Regulatory Affairs; Steven J. Miller, Ph.D., Executive Director, Cardiovascular Regulatory Affairs; and Robert J. Orzolek, Director, Regulatory Affairs.

We appreciate the Agency's prompt review of this application and the opportunity to discuss the FDA's views concerning alternative labeling language. Please contact me if you have any questions or require further information.

Sincerely,

Robert J. Orzolek
Director
Regulatory Affairs Department
(302) 886-4550
(302) 886-2822 (fax)

RJO/jr

Desk Copies: Ms. Sandra Birdsong, HFD No. 110, Room No. 5039
Ms. Zelda M. McDonald, HFD No. 110, Room No. 5024

Desk Copies: Ms. Sandra Birdsong
Division of Cardio-Renal
Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
ATTENTION: Document Control Room
HFD No. 110, Room No. 5039
1451 Rockville Pike
Rockville, MD 20852

Ms. Zelda M. McDonald
Division of Cardio-Renal
Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
ATTENTION: Document Control Room
HFD No. 110, Room No. 5024
1451 Rockville Pike
Rockville, MD 20852

DEC 1 - 1999

MEMORANDUM

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

DATE: DEC 1 1999

FROM: Director, Office of Drug Evaluation I, HFD-101

SUBJECT: ATLAS

TO: Director, Division of Cardio-Renal Drug Products, HFD-110

The FD&C Act refers to effects suggested in labeling, not solely to the Indications section. The proposed discussion of ATLAS is plainly an effectiveness claim and cannot be used if you believe ATLAS does not support a claim.

I note that there is no mention at all of doses in the CHF section of labeling (or in the post-infarction section). These could be added. ATLAS could be used to say that higher doses (to 40 mg) are tolerated.

I would like to discuss whether in this setting, the ATLAS is, in fact, persuasive on the combined death plus hospitalization endpoint.

Robert Temple, M.D.

cc:
Orig. NDA 19-777/S-037
HFD-110
HFD-110/Project Manager
HFD-101/R Temple
drafted:sb/12/1/99
filename:ZestrilAtlasMM.doc

NOV 29 1999

MEMORANDUM

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

DATE : November 29, 1999

FROM: Director, Division of Cardio-Renal Drug Product, HFD-110 Lipicky

SUBJECT: NDA 19-777/S-037, Lisinopril, ATLAS, Heart Failure, Zeneca Ltd.

TO: Director, Office of Drug Evaluation I, HFD-101

Sorry for getting this to you on short notice. This short fuse was caused by a combination of my being ill (again) and my thinking that I would sign the letter to the sponsor (the former unavoidable and the latter my mistake).

In short, the Division is convinced that the results of the ATLAS trial should be known to all health care practitioners who use lisinopril for the treatment of patients with heart failure. The current labeling has a dosage and administration section that says the highest dose for heart failure is 20 mg. That is clearly improper advice based upon the results of the ATLAS trial. Up to 40 mg a day is obviously safe enough in heart failure; current labeling for hypertension goes to 40 mg a day, so now there is no longer any empirical reason to make a distinction between the two diseases with respect to doses that may be used in treatment.

The Division is also convinced that (lacking placebo in ATLAS) one cannot conclude that there is a morbidity/mortality benefit of lisinopril when used for the treatment of patients with heart failure. So, there cannot be a firm basis for altering the Indications and Usage section. We think there should be firm basis for changes made to the Indications and Usage section; something more than "It is probably correct and makes good intuitive sense." The question is not, "Do I believe lisinopril has a morbidity/mortality benefit in patients with congestive heat failure?" The question is, "Do the data show that to be true.?" I think the data do not carry the day. I believed that lisinopril had a morbidity/mortality benefit even before ATLAS was conceived as a possible test of that hypothesis. ATLAS does not prove my belief to be true. It should not be treated as if it established that proof.

The Division once again endorses Dr. Chen's original proposal. The Heart Failure section of labeling has been re-edited (the most recent editing is attached). We think this clearly communicates the results of the ATLAS trial, as well as other trials that deal with heart failure. It is presented in appropriate context, and the wording suggested allows reasonable DDMAC control of promotion (although we have no written confirmation of the latter assertion from DDMAC. We have sent this memo and the attached labeling to DDMAC; they too have short notice).

In summary, the suggestion recommended by Dr. Chen should be carried out as conveyed in the attached labeling. The Clinical Pharmacology has been modified, Dosage and Administration has been modified to allow up to 40 mg a day in heart failure, and the How Supplied has been modified to provide for the 30 mg tablets. Indications and Usage has not been changed.

In the event that you disagree, the attached documentation and approvavable letter should still be sufficient to carry out your wishes. This is another one of those close calls. The regulatory implications are reasonably large. Your judgment need not be discussed by meeting. Do what you think best.

OFFICES OF DRUG EVALUATION
ORIGINAL NDA/NDA EFFICACY SUPPLEMENT
ACTION PACKAGE CHECKLIST

NDA# **19-777/S-037** Drug **Zestril (lisinopril)**

Applicant **Zeneca Pharmaceuticals** Chem/Ther/Other Types: **6S**

PM: **Sandy Birdsong** Phone: **594-5312** **HFD-110**

USER FEE GOAL DATE: **December 2, 1999** DATE CHECKLIST COMPLETED: **November 12, 1999**

	Arrange package in the following order (include a completed copy of this CHECKLIST):	Check or Comment
1.	ACTION LETTER with supervisory signatures Are there any Phase 4 commitments?	AP AE **X** NA Yes No **X**
2.	Have all disciplines completed their reviews? If no, what reviews are still in draft?	Yes **X** No
3.	LABELING (package insert and carton and container labels). (If final or revised draft, include copy of previous version with ODE's comments and state where in action package the Division's review is located. If Rx-to-OTC switch, include current Rx Package insert and HFD-312 and HFD-560 reviews of OTC labeling.)	Draft **X** Revised Draft Final
4.	Package inserts of the last 3 drugs approved that are of similar pharmacologic class.	**X**
5.	CLINICAL INVESTIGATOR FINANCIAL DISCLOSURE	**X**
6.	PATENT INFORMATION	**X**
7.	EXCLUSIVITY CHECKLIST	**X**
8.	PEDIATRIC PAGE (all NDAs)	**X**
9.	DEBARMENT CERTIFICATION (Copy of applicant's certification [all NDAs submitted after 1992]).	**X**
10.	Statement on status of DSI's AUDIT OF MAJOR CLINICAL STUDIES If AE or AP ltr, explain if not satisfactorily completed. Attach a COMIS printout of DSI status. If no audits were requested, include a memo explaining why.	
11.	REVIEWS [If more than 1 review for any 1 discipline, separate reviews with a sheet of: colored paper. Any conflicts between reviews must have resolution documented.]:	
	DIVISION DIRECTOR'S MEMO	
	GROUP LEADER'S MEMO	
	MEDICAL/STATISTICAL REVIEW	**X**
	SAFETY UPDATE REVIEW	
	BIOPHARMACEUTICS REVIEW	**X**
	PHARMACOLOGY REVIEW (include pertinent IND reviews)	
	Statistical Review of Carcinogenicity Study(ies)	
	CAC Report/Minutes	
	CHEMISTRY REVIEW	
	Labeling and Nomenclature Committee Review Memorandum	
	Date EER completed (attach signed form or CIRTS printout)	OK No
	FUR needed FUR requested	
	Have methods been validated?	Yes (attach) No
	Environmental Assessment Exclusion?	
	If no exclusion, Review/FONSI	
	MICROBIOLOGY REVIEW	
	What is the status of the monograph?	
12.	CORRESPONDENCE and FAXes	**X**
13.	Minutes of Meetings including Telecons and Memoranda	
	Date of End-of-Phase 2 Meeting-None	
	Date of pre-IND Meeting-None	
14.	ADVISORY COMMITTEE MEETING MINUTES or, if not available, 48-hour Info Alert or pertinent section of transcript	Minutes **NA** Info Alert Transcript No Mtg
15.	FEDERAL REGISTER NOTICES; OTC or DESI DOCUMENTS	**NA**
16.	If approval letter, has ADVERTISING MATERIAL been reviewed? If no and this is an AP with draft labeling letter, has advertising material already been requested?	Yes No Yes, documentation attached No, included in AP ltr
17.	INTEGRATED SUMMARY OF EFFECTIVENESS (from NDA)	**NA, only one study**
18.	INTEGRATED SUMMARY OF SAFETY (from NDA)	**NA, only one study**

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NDA 19-777/S-037

AUG 5 1999

Zeneca Pharmaceuticals
Attention: Mr. Robert J. Orzolek
1800 Concord Pike
P.O. Box 15437
Wilmington, DE 19850-5437

Dear : Mr. Orzolek

Please refer to your supplemental new drug application for Zestril (lisinopril) 2.5, 5, 10, 20, 30 and 40 mg Tablets.

In reviewing your submission of January 29 and July 15, 1999 our Biopharmacist has the following comments that require your attention:

1. This bioequivalence study is acceptable to the Office of Clinical Pharmacology and Biopharmaceutics. The new 30mg lisinopril tablet is bioequivalent to 3 x 10mg lisinopril tablets that were used in pivotal clinical efficacy studies. This conclusion is based on the 90% confidence intervals for the ratio of AUC (0-t), AUC (0-inf), and Cmax between treatments. Also, both treatments had a median Tmax value of 6 hours. All 90% confidence intervals were within the 0.80 to 1.25 range generally required to show bioequivalence.

2. Please adopt and apply the currently established dissolution method and specification, used for other strengths of lisinopril tablets, to the new 30mg tablet:

Method:	Apparatus II (paddle)
Speed:	50 rpm
Medium:	900mL 0.1 N hydrochloric acid
Specs:	Q not less than 80% in 30 minutes

If you have any questions, please contact:

Zelda McDonald
Regulatory Health Project Manager
(301) 594-5333

Sincerely yours,

RJL 9/5/99

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Archival NDA 19-777/S-037
HFD-110 /division file
HFD-110 /Z McDonald
HFD-110 /Team Leaders and reviewers
Drafted by: zm/7/28/99
Initialed by: T Parmelee/7/29/99
P Marroum/7/29/99
J Short/7/29/99
K Srinivasachar/7/29/99
Final: asb/8/2/99
filename: 19777gcS037.DOC

GENERAL CORRESPONDENCE

ZENECA

Pharmaceuticals

A Business Unit of Zeneca Inc.
Drug Regulatory Affairs Department
Wilmington, DE 19850-5437

RAPIFAX RAPIFAX RAPIFAX

DATE: 7-15-99

PAGES TO FOLLOW THIS LEAD SHEET: 6

RAPIFAX MESSAGE FOR: Thomas A. Parmalee, FDA

RAPIFAX MESSAGE FROM: Bob Orwolek

PLEASE MAKE COPIES FOR:

Requested bioequivalence data NDA 19-777/S-037

Please confirm Rapifax to 1-302-886-2822 - Thank You

ZENECA Pharmaceuticals
A Business Unit of Zeneca Inc.
1800 Concord Pike
P.O. Box 15437
Wilmington, DE 19850-5437

ZENECA

SENT UPS NEXT DAY AIR

JUL 15 1999

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, Room No. 5039
1451 Rockville Pike
Rockville, MD 20852

Dear Dr. Lipicky:

Re: ZESTRIL® (lisinopril) Tablets
NDA 19-777/S-037
Response to FDA Request for Information - Bioequivalence Data

Reference is made to telephone conversations of July 8 and 13, 1999 between Raman K. Baweja and Thomas A. Parmelee of the FDA, and Robert J. Orzolek of Zeneca Pharmaceuticals during which the Agency requested that additional data be submitted with regard to a bioequivalence study (1262IL/0027) included in the above referenced supplemental application.

The Agency requested that Zeneca provide data establishing AUC (0 to infinity) for each subject in the bioequivalence study, the % extrapolation AUC (t-infinity), and the 90% confidence intervals for AUC (0 to infinity). Accordingly, attached hereto is the requested AUC(0 to infinity) data which were log-transformed prior to analysis.

Please contact me if you have any questions or require further information.

Sincerely,

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

RJO/jr
Enclosures

Desk Copies: Raman K. Baweja, HFD No. 860, Room No. 4071
Thomas A. Parmelee, HFD No. 860, Room No. 5048
Zelda M. McDonald, HFD No. 110, Room No. 5024

Results from analysis of AUC(0-infinity) for trial 1262IL/0027

Assumptions of Normality and consistency of variance were met in this analysis.

The summary of AUC(0-inf) is presented in Table 1, whilst the results of the analysis are presented in Table 2.

Table 1 AUC(0-inf) of lisinopril after 30 mg lisinopril and 3x10 mg placebo or 3x10 mg lisinopril and 30 mg placebo.

Lisinopril formulation	n	AUC(0-t) (ng·h/ml) Gmean	CV
30 mg lisinopril and placebo 3x10 mg	35	1735.297	44.845
3x10 mg lisinopril and placebo 30 mg	36	1699.489	47.882

Gmean Geometric mean
n Number of volunteers assessed
AUC(0-inf) Area under the curve from zero to infinity
CV Coefficient of variation

Table 2 Statistical comparison AUC(0-inf) for the analysis of 30 mg lisinopril and 3x10 mg placebo versus 3x10 mg lisinopril and 30 mg placebo.

Comparison	30 mg lisinopril and 3x10 mg placebo		3x10 mg lisinopril and 30 mg placebo		Ratio of glsmeans[a]	90%CI for ratio[a]
Parameter	Glsmean	N	glsmean	n		
AUC(0-inf) (ng.h/ml)	1724.05	35	1699.49	36	1.01	0.93 to 1.11

[a] Ratio and 90% CI expressed as ratio of 30mg lisinopril and 3x10mg placebo/3x10mg lisinopril and 30mg placebo
glsmean Geometric least squares mean
C_{max} Maximum serum concentration
AUC(0-inf) Area under the curve from zero to infinity

For the analysis of AUC(0-inf), the formulation-by-sex interaction term was not included in the statistical model as was it was found to be non-significant ($p > 0.05$). In addition, the effects of treatment sequence and period and the main effect of sex were not statistically significant.

This analysis shows that the 90% confidence interval for the comparison of the two formulations was within the protocolled limits for equivalence of 0.8 to 1.25. It is therefore possible to conclude equivalence between 30 mg lisinopril (with 3x10 mg placebo) and 3x10 mg lisinopril (with 30 mg placebo) for AUC(0-inf).

In addition, an analysis was performed excluding the data for volunteer 0001/0027 as this volunteer was considered to have a significant protocol violation (see Clinical Trial Report). The resulting 90% confidence interval was between 0.8 and 1.25, as with the main analysis.

Satisfactory tablets with low friability and rapid disintegration times could be obtained over a wide range of compression pressures (see Table 1).

The dissolution results of tablets compressed to a hardness near and above the projected mean tablet hardness limit are presented below in Table 2. They indicate the satisfactory release of the lisinopril was achieved even at extreme compression pressures.

Table 2 Dissolution of ZESTRIL 30 mg batches at high tablet hardnesses

Batch No	Tablet hardness (kp)	Disintegration time (mins)	Mean % dissolution at 15 mins (RSD)	Mean % dissolution at 30 mins (RSD)
P/0022/06A	11.5	1.17	94 (5.5)	100 (2.4)
P/0022/06B	14.8	2.33	93 (5.2)	100 (0.5)

The dissolution profiles of ZESTRIL 30 mg tablets and ZESTRIL 3 x 10 mg tablets were compared. The results are presented in Table 3, and a similarity factor value was calculated as described in the SUPAC Immediate Release Guidance (Federal Register, 30 November 1995, pp 61638 - 61643). A similarity factor value of 75.75 was obtained confirming the two dissolution profiles as similar.

Table 3 Mean dissolution results (% w/w) for three ZESTRIL 10 mg tablets and a single ZESTRIL 30 mg tablet

	ZESTRIL 30 mg Bx 13301 (single tablet)		ZESTRIL 10 mg Bx CRF900 (three tablets)	
Sampling time (minutes)	Mean dissolution (% w/w)	Standard deviation (%)	Mean dissolution (% w/w)	Standard deviation (%)
15	95	2.1	88	3.8
30	99	1.2	99	1.1
45	100	0.8	99	1.2
60	100	0.7	99	1.2
120	101	0.7	100	1.3

5.3 Manufacturing formula

Batch quantities and process flow are unchanged from the approved 20 mg process. They are repeated here for convenience.

Table 5 Batch quantities

	mg/tablet	Quantity per batch (kg)
Lisinopril USP		
Mannitol USP		
Calcium Phosphate		
[ ]		
[ ]		
Ferric Oxide[2] USNF		
[ ]		
Corn Starch USNF		
Magnesium Stearate USNF		

1 [ ]

2 [ ]

3 [ ]

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On Original