CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 019777 /S032

Trade Name : ZESTRIL TABLETS

Generic Name: Lisinopril Tablets

Sponsor : Zeneca Pharmaceuticals

Approval Date: January 8, 1997
Application Number 019777/S032

APPROVAL LETTER
Dear Dr. Kennedy:

Please refer to your December 3, 1996 supplemental new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zestril (lisinopril) 2.5, 5, 10, 20, and 40 mg Tablets.

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

**CLINICAL PHARMACOLOGY, Pharmacodynamics and Clinical Effects, Heart Failure:** The last sentence has been revised to add the following to the end of this subsection:

> 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.

**CLINICAL PHARMACOLOGY, Pharmacodynamics and Clinical Effects, Acute Myocardial Infarction:** As we requested in our letter dated November 24, 1995, in the first sentence of the fourth paragraph, the word "a" has been revised to "the" in the phrase "consisting of the number of patients who had ... ."

**WARNINGS, Anaphylactoid and Possibly Related Reactions, Anaphylactoid reactions during membrane exposure:** The phrase "(a procedure dependent upon devices not approved in the United States)" has been deleted, as we requested in our facsimile dated March 8, 1996.

**WARNINGS, Hypotension:** As we requested in our letter dated November 24, 1995, "e.g.," has been added before "systolic blood pressure of 100 mm Hg or lower" in the second sentence of the fourth paragraph.

**PRECAUTIONS, Pediatric Use:** The word "children" has been replaced with "pediatric patients" as required by the regulations on the revision of the Pediatric Use subsection of the labeling [21 CFR 201.57 (f)(9)].
HOW SUPPLIED: To comply with the CDER Stability Committee Uniform Storage Statement, the first sentence of the fourth paragraph has been revised to "Store at controlled room temperature, 20-25° C (68-77° F) [see USP]."

We have completed the review of this supplemental application and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the final printed labeling included with your December 3, 1996 submission. Accordingly, the supplemental application is approved effective on the date of this letter.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact:

Ms. Kathleen Bongiovanni
Regulatory Health Project Manager
(301) 594-5334

Sincerely yours,

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 019777/S032

FINAL PRINTED LABEL
Lisinopril is a white to off-white, crystalline powder, with a molecular weight of 641.3. It is soluble in water and sparingly soluble in methyl and practically insoluble in ethanol. Lisinopril is supplied as 5 mg, 10 mg, 20 mg and 40 mg tablets for oral administration.

CLINICAL PHARMACOLOGY

Mechanism of Action: Lisinopril inhibits angiotensin converting enzyme (ACE), which is present in vascular tissue and the kidney. ACE is a peptidyl dipeptidase and nonselective, irreversible, and competitive inhibitor of ACE.

The angiotensin-converting enzyme (ACE) is responsible for the conversion of angiotensin I to angiotensin II, a potent vasoconstrictor and aldosterone secretagogue. Angiotensin II is also known to stimulate aldosterone secretion and is a potent vasoconstrictor.

The inhibition of ACE by Lisinopril results in the reduction of plasma renin activity and consequently in a decrease in plasma aldosterone levels. This effect is more pronounced in patients with impaired renal function.

Other effects of ACE inhibition include the following:

- Reduction of blood pressure
- Decrease in plasma renin activity
- Decrease in aldosterone levels
- Decrease in systemic vascular resistance
- Increase in cardiac output
- Increase in plasma volume
- Increase in red blood cell mass
- Decrease in peripheral vascular resistance

It is important to note that the effects of ACE inhibition are generally reversible on discontinuation of the drug.
indications and usage

Hypertension. Zestril is indicated for the treatment of hypertension. It may be used alone or in combination with one of the following classes of antihypertensive agents.

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

Acute Myocardial Infarction: Zestril is indicated for the treatment of hemodynamically stable patients within 24 hours of acute myocardial infarction. In addition, patients should receive an adequate trial of recommended inotropic agents such as thiamylal, anesthetics and beta-blockers.

In using Zestril, consideration should be given to the fact that another angiotensin-converting enzyme inhibitor, captopril, has caused angioedema, particularly in patients with a history of alveolar or angioneurotic edema. Patients seeking ACE inhibitors (including Zestril) may be subject to a variety of angioedema-like reactions.

Anaphylaxis: 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 and 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 angioneurotic edema related to previous treatment with an angiotensin converting enzyme (ACE) inhibitor. Zestril is not recommended for use in patients with a history of angioedema during previous treatment with ACE inhibitors.

WARNINGS

Anaphylactic and Related Reactions: Panhypopituitarism, and especially angiotensin-converting enzyme inhibiting agents affect the metabolism of corticosteroids and mineralocorticoids. Patients receiving ACE inhibitors (including Zestril) may experience an acute reduction in aldosterone secretion and serum potassium concentration.

Anaphylactic reactions during hemodialysis procedures and potentially mast-cell degranulated anaphylactoid reactions have been reported in Zestril patients. In similar reactions, patients were treated with aminophylline, epinephrine, and supportive care including fluid resuscitation.

Anaphylactoid Reactions During Membrane Oxygenators: Severe and potentially fatal anaphylactoid reactions have been reported in patients undergoing extracorporeal membrane oxygenation procedures. In some patients, these reactions were avoided when ACE inhibitors were administered as a single intravenous bolus dose prior to membrane oxygenation.

Hypokalemia: Hypokalemia may occur in patients who are being treated with Zestril. In patients with a history of hypokalemia, it may cause hyperkalemia. In patients with metabolic acidosis, hyperkalemia may cause hyperkalemia, and the patient's potassium level should be monitored carefully.

In patients with chronic renal failure, a potentially severe hyperkalemia may occur with concurrent administration of potassium-sparing diuretics, metolazone and furosemide. In hemodialysis patients, the possibility of hyperkalemia should be considered, particularly when the patient is receiving a potassium-sparing diuretic (see also ADVERSE REACTIONS).

Hypokalemia is defined as serum potassium concentration exceeding 5 mmol/L. In patients with chronic renal failure, hyperkalemia may occur with concurrent administration of potassium-sparing diuretics or metolazone and furosemide. In hemodialysis patients, the possibility of hyperkalemia should be considered, particularly when the patient is receiving a potassium-sparing diuretic (see also ADVERSE REACTIONS).

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ZESTRIL (losartan)

Losartan is a selective inhibitor of angiotensin II receptor (AT1). When given concomitantly with ACE inhibitors, Losartan can be used to reduce the incidence of hypertension in patients with hypertension who are receiving angiotensin-converting enzyme (ACE) inhibitors. Losartan is also effective in the treatment of hypertension and is recommended as a secondary drug in patients with hypertension who are not responsive to other antihypertensive agents.

Drug Interactions

Losartan is metabolized by the cytochrome P450 3A4 enzyme. It is therefore important to avoid concomitant use of other drugs that can inhibit this enzyme or increase its activity. Losartan is not known to interact with any other drugs, and no specific interactions have been reported.

Adverse Effects

The most common adverse effects of Losartan are dizziness, headache, diarrhea, and nausea. Other less common adverse effects include fatigue, asthenia, and anemia. These adverse effects are generally mild and do not require discontinuation of treatment. In patients with renal impairment, Losartan should be used with caution, and the dosage should be reduced accordingly.

Dosages

The usual adult dose of Losartan is 50 mg once daily, with the maximum daily dose being 100 mg. The dosage may be increased to 200 mg/day if needed. Children under 6 years of age should receive a lower dose based on body weight. The use of Losartan in children under the age of 6 years is not recommended.

Special Populations

Losartan is generally well tolerated in all age groups, including children. However, it is not recommended for use in children under the age of 6 years. In patients with renal impairment, the dosage should be reduced accordingly. Losartan is not recommended for use in patients with hepatic impairment.

It is important to consult the full prescribing information for Losartan before initiating treatment. The full prescribing information contains additional information on dosages, precautions, and adverse effects.

Losartan is contraindicated in patients with severe renal impairment (creatinine clearance <30 mL/min) or hepatic impairment. It is also contraindicated in patients with a history of allergy to losartan or to other drugs in the angiotensin II receptor antagonist class.

ZESTRIL (enalapril)

Enalapril is a converting enzyme inhibitor (ACE inhibitor). It is used to treat hypertension and to reduce the risk of cardiovascular events in patients with hypertension and diabetes. Enalapril is also effective in the treatment of congestive heart failure and is recommended as a secondary drug in patients with hypertension who are not responsive to other antihypertensive agents.

Drug Interactions

Enalapril is metabolized by the hepatic cytochrome P450 2C9 enzyme. It is therefore important to avoid concomitant use of other drugs that can inhibit this enzyme or increase its activity. Enalapril is not known to interact with any other drugs, and no specific interactions have been reported.

Adverse Effects

The most common adverse effects of Enalapril are dizziness, headache, and nausea. Other less common adverse effects include fatigue, asthenia, and anemia. These adverse effects are generally mild and do not require discontinuation of treatment. In patients with renal impairment, Enalapril should be used with caution, and the dosage should be reduced accordingly.

Dosages

The usual adult dose of Enalapril is 2.5 mg once daily, with the maximum daily dose being 20 mg. The dosage may be increased to 5 mg/day if needed. Children under 6 years of age should receive a lower dose based on body weight. The use of Enalapril in children under the age of 6 years is not recommended.

Special Populations

Enalapril is generally well tolerated in all age groups, including children. However, it is not recommended for use in children under the age of 6 years. In patients with renal impairment, the dosage should be reduced accordingly. Enalapril is also contraindicated in patients with a history of allergy to enalapril or to other drugs in the converting enzyme inhibitor class.

It is important to consult the full prescribing information for Enalapril before initiating treatment. The full prescribing information contains additional information on dosages, precautions, and adverse effects.

Enalapril is contraindicated in patients with severe renal impairment (creatinine clearance <30 mL/min) or hepatic impairment. It is also contraindicated in patients with a history of allergy to enalapril or to other drugs in the converting enzyme inhibitor class.
Dosage and Administration

Hydralazine

Initial Therapy: In patients with uncomplicated essential hypertension not on antihypertensive 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 may be improved by measuring blood pressure just prior to dosing to determine whether satisfactory control is being maintained for 24 hours. If it is, an increase in dose should be considered. Doses of 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.

In the management of hypertension, 2.0% of patients receiving ZESTRIL discontinued therapy due to labile blood pressure responses; 1.5% required discontinuation due to clinical symptoms of heart failure. See DOSAGE AND ADMINISTRATION, Presyncope and Syncope.

ZESTRIL is contraindicated in patients with a history of angioedema associated with Zestril.

ZESTRIL should be used with caution in patients with renal artery stenosis and in patients with decreased renal function. In patients with renal failure, dosages of ZESTRIL should be reduced by 50% or more.

ZESTRIL is contraindicated in patients with a history of angioedema associated with Zestril.

Dosage and Administration

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

Administered Therapy: The usual dosage is 20 mg once daily. Dosage may be increased up to a maximum of 40 mg daily.

Renal Failure

Creatinine Clearance

Initial Dose

Normal Renal Function

Mild Impairment

Marked to Severe Impairment

Diabetic Patients

*See WARNINGS, Analytical Reactions During Membrane Exposure.

Dosage should be adjusted depending on the blood pressure response.

ZESTRIL is indicated as an additive therapy with diuretics and digitalis.

Nephrotic Syndrome

The recommended dosage is 0.5 mg per day. When starting therapy with hydralazine in patients with a history of angioedema, the initial dose should be administered under medical observation, preferably in those patients with low blood pressure (systolic blood pressure below 100 mm Hg). The mean peak blood pressure lowering occurs in eight hours after dosing. Observation should continue until blood pressure is stable. The concomitant diuretic dose should be decreased, if possible, to help minimize hypertension 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 dose range is 5 to 20 mg per day administered as a single daily dose.

Dosage Adjustment in Tolbutamide and Frusemide

The blood pressure lowering effect of ZESTRIL is additive with tolbutamide and frusemide. In patients with a history of angioedema, the initial dose should be administered under medical observation, and the dose increased gradually as tolerated. After the initial dose of ZESTRIL, the usual effective dose range is 10 to 20 mg per day administered.

If angioedema has occurred in patients receiving ZESTRIL (0.5% to 1.0% of patients), angioedema has occurred in patients with a history of angioedema associated with Zestril. In the initial dose of ZESTRIL, the usual effective dose range is 5 to 20 mg per day administered as a single daily dose.

Dosage Adjustment in Patients with Heart Failure and Renal Impairment

In patients with heart failure who have had angioedema associated with Zestril, the usual effective dose range is 5 mg per day, followed by 5 mg every 4 hours, or 20 mg per day in patients with angioedema associated with Zestril. In patients with a history of angioedema associated with Zestril, the usual effective dose range is 5 to 20 mg per day administered as a single daily dose.

The usual effective dose range is 5 to 20 mg per day administered as a single daily dose.

ZESTRIL is contraindicated in patients with angioedema associated with Zestril.
CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 019777/S032

LABELING REVIEW
RHPM Review of Labeling

NDA: 19-777/S-032 Zestril (lisinopril) Tablets

Date of submission: December 3, 1996
Date of receipt: December 4, 1996
Applicant: Zeneca Pharmaceuticals Group

Background: Based on the labeling for NDA 19-915/S-009 Monopril (fosinopril sodium) Tablets for the treatment of CHF (approved May 2, 1995), we issued supplement request letters on May 4, 1995 for ACE inhibitors approved for the treatment of CHF with once-daily dosing (Prinivil and Zestril), asking for the following labeling change:

Clinicical Pharmacology, Pharmacodynamics and Clinical Effects, Heart Failure:
Please add the following as the last sentence in this subsection:
The once daily dosage for the treatment of congestive heart failure is a consequence of being the only dosage regimen used during clinical trial development and does not represent a known optimum dosage schedule.

Zeneca responded with a submission dated November 8, 1995. We issued a second supplement request letter dated December 1, 1995, asking for revision of the above sentence to:
The once daily dosage for the treatment of congestive heart failure was the only dosage regimen used during clinical trial development and was determined, perhaps erroneously, by the measurement of hemodynamic responses.

Zeneca responded with a submission dated February 1, 1996. We sent out a third supplement request letter dated May 1, 1996, asking for revision of the above sentence to:
The once daily dosage 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 responses.

Zeneca has responded with this supplement. In addition to the above statement, they have included revisions requested in our November 24, 1995 approval letter for S-023, our facsimile transmission of March 8, 1996, the regulations on pediatric labeling, and the November 16, 1995 CDER Stability Committee Uniform Storage Statement Memorandum.

Review: The submitted final printed labeling has been revised as follows:

Clinical Pharmacology, Pharmacodynamics and Clinical Effects, Heart Failure:
The last sentence has been revised to add the following to the end of this subsection:
"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."

Clinical Pharmacology, Pharmacodynamics and Clinical Effects, Acute Myocardial Infarction:
As we requested in our letter dated November 24, 1995, in the first sentence of the fourth paragraph, the word "a" has been revised to "the" in the phrase "consisting of the number of patients who had ..."
WARNINGS, Anaphylactoid and Possibly Related Reactions, Anaphylactoid reactions during membrane exposure:
   The phrase "(a procedure dependent upon devices not approved in the United States)"
   has been deleted, as we requested in our facsimile dated March 8, 1996.

WARNINGS, Hypotension:
   As we requested in our letter dated November 24, 1995, "e.g.," has been added before "systolic blood pressure of 100 mm Hg or lower" in the second sentence of the fourth paragraph.

PRECAUTIONS, Pediatric Use:
   The word "children" has been replaced with "pediatric patients" as required by the regulations on the revision of the Pediatric Use subsection of the labeling [21 CFR 201.57 (f)(9)].

HOW SUPPLIED:
   To comply with the CDER Stability Committee Uniform Storage Statement, the first sentence of the fourth paragraph has been revised to "Store at controlled room temperature, 20-25° C (68-77° F) [see USP]."

Recommendation: I will prepare an approval letter for Dr. Lipicky's signature. This supplement falls under 21 CFR 314.70(b), Supplements requiring FDA approval before the change is made.

Kathleen F. Bongiovanni 12-23-96

cc:
   19-777/S-032
   HFD-110
   HFD-111/KBongiovanni
   HFD-111/SBenton

kb/12/23/96.
CHEMISTRY REVIEW
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<td>Wilmington, DE 19850-5437</td>
<td>3 Dec 96</td>
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<td>Final Printed Labeling (FPL) for a revised Package Insert (PI).</td>
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<tr>
<td>Changes have been made in the following sections in compliance with requests from the Agency:</td>
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<tr>
<td>(1) CLINICAL PHARMACOLOGY - Pharmacodynamic and Clinical Effects, Heart Failure</td>
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<tr>
<td>(2) CLINICAL PHARMACOLOGY - Pharmacodynamic and Clinical Effects, Acute Myocardial Infarction</td>
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<td>(3) WARNINGS - Anaphylactoid Reactions During Membrane Exposure</td>
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<td>(4) WARNINGS - Hypotension</td>
</tr>
<tr>
<td>(5) PRECAUTIONS - Pregnancy, Pediatric Use</td>
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<tr>
<td>(6) HOW SUPPLIED - The storage statement is changed to read: &quot;Store at controlled room temperature, 20-25°C (68-77°F) [See USP].&quot;</td>
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The revised PI is designated "Rev J 08/96."

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<tr>
<td>Name</td>
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<tr>
<td>James H. Short</td>
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<tr>
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<td>9 Dec 96</td>
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