Application Number: NDA 19777/S035
NDA 19-777/S-035

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

Dear Dr. Kennedy:

Please refer to your supplemental new drug application dated October 15, 1998, received October 15, 1998, 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.

We acknowledge receipt of your submissions dated December 22, 1998 and January 8, 1999.

This supplemental new drug application provides for the manufacture of a new tablet strength, 30 mg, at the Carolina, Puerto Rico plant, and for final printed labeling revised as follows:

DESCRIPTION: The third and fifth paragraphs have been revised to include "30 mg."

HOW SUPPLIED: The following has been added:
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.

At the end of the package insert,
"Manufactured by: IPR Pharmaceuticals Inc.
Distributed by:
Zeneca Pharmaceuticals
A Business Unit of Zeneca Inc.
Wilmington, DE 19850-5437"

has been revised to:
"ZENECA
Manufactured for:
Zeneca Pharmaceuticals
A Business Unit of Zeneca Inc.
Wilmington, Delaware 19850-5437
By: IPR Pharmaceuticals, Carolina, Puerto Rico"

We have completed the review of this supplemental application, as amended, 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 submitted final printed package insert included in your December 22, 1998 submission and the container labels included in the January 8, 1999 submission. Accordingly, the supplemental application is approved effective on the date of this letter.

Please submit one market package of the drug product when it is available.
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

cc: Archival NDA 19-777  
HFD-110/Div. Files  
HF-2/MedWatch (with labeling)  
HFD-002/ORM (with labeling)  
HFD-101/ADRA (with labeling)  
HFD-40/DDMAC (with labeling)  
HFD-613/OGD (with labeling)  
HFD-95/DDMS (with labeling)  
HFD-810/DNDC Division Director  
DISTRICT OFFICE  
HFD-110/K.Bongiovanni  
sh/1/12/99;1/20/99  
Initialed by: J Short/1/12/99  
J Koerner/1/12/99  
C Resnick/1/12/99  
S Chen/1/13/99  
N Morgenstern/1/13/99  
filename: 19777s035ap.doc

APPROVAL (AP)  

1-20-99
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19777/S035

APPROVABLE LETTER
NDA 19-777/S-035

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

Dear Dr. Kennedy

Please refer to your supplemental new drug application dated October 15, 1998, received October 15, 1998, 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.

This supplement provides for the manufacture of a new tablet strength, 30 mg, at the Carolina, Puerto Rico plant and draft labeling revised as follows:

DESCRIPTION: The third and fifth paragraphs have been revised to include "30 mg."

HOW SUPPLIED: The following has been added:
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.

At the end of the package insert,
"Manufactured by: IPR Pharmaceuticals Inc.
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Zeneca Pharmaceuticals
A Business Unit of Zeneca Inc.
Wilmington, DE 19850-5437"
has been revised to:
"ZENECA
Manufactured for:
Zeneca Pharmaceuticals
A Business Unit of Zeneca Inc.
Wilmington, Delaware 19850-5487
By: IPR Pharmaceuticals, Carolina, Puerto Rico"

We have completed the review of this application 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 package insert and immediate container and carton labels included in the October 15, 1998 submission with the following exception:

At the end of the package insert, in the address for Zeneca Pharmaceuticals, please revise the zip code to "19850-5437."

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.
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.

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.

We remind you that, after approval of this supplemental application, you may not market the 30 mg tablet in bottles of 1000 tablets unless you include this package configuration in the HOW SUPPLIED section of the package insert. This change in labeling may be described in your next annual report (see 21 CFR 314.70(d)(2)).

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. 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

cc:
Archival NDA 19-777
HFD-110/Div. Files
HFD-95/DDMS
DISTRICT OFFICE
HFD-110/K.Bongiovanni
sb/12/7/98; 12/7/98; 12/17/98
Initialled by: J Short/12/8/98
K Srinivasachar/12/8/98
J Koerner/12/8/98
C Resnick/12/9/98
S Chen/12/15/98
N Morgenstern/12/15/98

filename: 19777s035ae.doc

APPROVABLE (AE)
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19777/S035

FINAL PRINTED LABELING
USE IN PREGNANCY

When used in pregnancy during the second and third trimesters, ZELSTRAN should be discontinued as soon as possible. See WARNINGS, Teratogenicity and Mutagenicity.

DESCRIPTION

ZELSTRAN is a white or off-white, crystalline powder, with a molecular weight of 483.53. It is soluble in water and sparingly soluble in ethanol and practically insoluble in ether.

ZELSTRAN 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—carbomer, magnesium stearate, mannitol, lactose, talc. 5, 10, 20 and 30 mg tablets—lactose, magnesium stearate, mannitol, microcrystalline cellulose, talc, yellow lacquer.

CLINICAL PHARMACOLOGY

Mechanism of Action: ZELSTRAN inhibits angiotensin converting enzyme (ACE) in human subjects and animals. ACE is a peptide degrading enzyme, which catalyzes the conversion of angiotensin I to angiotensin II. This enzyme also degrades some substances, such as bradykinin and substance P. ZELSTRAN also stimulates the production of nitric oxide (NO), which is a vasodilator. The beneficial effects of ZELSTRAN on blood pressure and heart failure are due to the inhibition of the renin-angiotensin-aldosterone system. The inhibition of NO production is a consequence of the decreased activity of NO synthase. The use of ZELSTRAN results in decreased aldosterone secretion and increased aldosterone excretion. This effect may contribute to increased sodium and water retention.

ZELSTRAN has been shown to lower blood pressure in patients with normal renal function treated with ZELSTRAN alone. The reduction in blood pressure is dose dependent.

ZELSTRAN is associated with a marked increase in urine volume and a decrease in urine sodium excretion. The response to ZELSTRAN is rapid, and the maximum effect is observed within 1 hour after administration.

ZELSTRAN has been shown to be effective in the treatment of hypertension in both the short- and long-term treatment of hypertension.

Acute Hypertensive Intolerance: The Gugino failure is an acute, life-threatening condition that occurs in some patients treated with ZELSTRAN. It is characterized by a sudden, severe increase in blood pressure and heart rate, which can lead to cardiovascular collapse. In some cases, this reaction can lead to death.

The mechanism by which ZELSTRAN intolerance occurs is not well understood. However, it is believed that ZELSTRAN intolerance occurs in patients who are susceptible to the drug's effects on the renin-angiotensin-aldosterone system.

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The mechanism by which ZELSTRAN intolerance occurs is not well understood. However, it is believed that ZELSTRAN intolerance occurs in patients who are susceptible to the drug's effects on the renin-angiotensin-aldosterone system.
Patient with acute myelogenous leukemia treated with ZESTRIL has a higher (9.0% versus 3.7%) incidence of persistent hemolytic anemia (biotin deficiency), 34.5% of patients with ZESTRIL and 15.9% of patients with placebo treatment. There was no significant difference in the incidence of hepatic dysfunction (3.2% versus 1.9%) in patients receiving ZESTRIL and placebo, respectively. The incidence of nausea and vomiting was the same in both treatment groups.

Increased Renal Function: A consequence of withholding the renoprotective effect of angiotensin II blockade is the severe and potentially life-threatening complication of acute renal failure with resultant renal dysfunction and death. Therefore, it is important to initiate treatment with ACE inhibitors immediately, as early as possible.

Renal Function: ACE inhibition is characterized by a rapid diuresis and natriuresis, which is usually associated with increased glomerular filtration rate (GFR) and renal plasma flow (RPF). The diuresis and natriuresis are generally not associated with significant changes in blood pressure, because of the concomitant reduction in intravascular volume. In addition, ACE inhibitors have been shown to improve renal function in patients with chronic renal insufficiency and diabetes.

Renal Function: ACE inhibitors are 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. Any angiotensin-converting enzyme inhibitors may cause significant adverse reactions, some of which may be life-threatening. Anaphylactic or Anaphylactoid Reactions: Anaphylactic or anaphylactoid reactions have been reported in patients treated with ACE inhibitors. These reactions are characterized by a rapid onset of hypotension, fever, flushing, and angioedema.

Anaphylaxis: Anaphylactic or anaphylactoid reactions have been reported in patients treated with ACE inhibitors. These reactions are characterized by a rapid onset of hypotension, fever, flushing, and angioedema. Anaphylaxis can occur in patients with no previous history of angioedema.

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ZESTRIL (lisinopril)

vomiting or diarrhea may also lead to a loss of blood pressure; patients should be advised to consult their physician.

Hypokalemia: Patients should be told that loss of potassium may occasionally experience an exacerbation of blood pressure after withdrawal of ACE inhibitors. The prophylactic effects of ZESTRIL can be minimized by discontinuing the diuretic or increasing the dosage of potassium supplements. If an effect is necessary to continue the diuretic, inhaled therapy with ZESTRIL at a dose of 1.25 mg/day is recommended. A diuretic can be discontinued when the potassium level 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 each can be reduced when it is given with a diuretic. (See DOSAGE AND ADMINISTRATION.)

Carcinogenesis, Mutagenesis, Impairment of Fertility: There was no evidence of clastogenic effect when lisinopril was administered for 105 weeks to male and female rats at doses up to 90 mg/kg/day (62 times the maximum recommended daily human dose). This was also the same for clastogenic effect in mice. There was no evidence of clastogenic effect when lisinopril was administered for 105 weeks to male and female rats at doses up to 125 mg/kg/day (64 times the maximum recommended daily human dose). This was 9.5 times the maximum recommended daily human dose. There was no evidence of carcinogenic potential in the mouse and rat studies. There were no adverse effects on reproductive performance in rats and mice treated up to 50 mg/kg/day. This dose is 188 times and 50 times the maximum human dose when based on body weight and body surface area, respectively.

Dosage and Administration: ZESTRIL has been found to be generally well tolerated in controlled clinical trials involving 1800 patients with hypertension or heart failure. The incidence of adverse events was mild and transient.

Hypotension: In clinical trials in patients with hypertension treated with ZESTRIL, discontinuation of therapy due to adverse effects was observed at least 5% or at a dose of 10 mg/day. Frequency of adverse effects could not be related to total dosage changes within the recommended therapeutic dose range.

For adverse effects occurring in greater than 1% of patients with hypertension treated with ZESTRIL, more frequent than in placebo-treated patients, dosage increases were not recommended. In the case of adverse effects occurring in less than 1%, it was decided to continue therapy in the hope that the beneficial effects of ZESTRIL would outweigh the inconvenience caused by the adverse effects. (See WARNINGS, and DOSAGE AND ADMINISTRATION.)
APPLICATION NUMBER: NDA 19777/S035

CHEMISTRY REVIEW(S)
**CHEMIST'S REVIEW**

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<thead>
<tr>
<th>1. ORGANIZATION</th>
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<th>3. Name and Address of Applicant (City &amp; State)</th>
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<td>Wilmington, DE 19850-5437</td>
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<td>S-035</td>
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<td>15 Oct 98</td>
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<th>5. Drug Name</th>
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<td>Zestril</td>
<td>Lisinopril</td>
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<th>7. Amendments &amp; Other (reports, etc) - Dates</th>
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<td>Amendment 22 Dec 98</td>
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<th>8. Supplement Provides For: Manufacture of a 30 mg tablet.</th>
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<th>9. Pharmacological Category</th>
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<tr>
<td>NDA 19-558 Prinivil, Merck</td>
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<tr>
<th>12. Dosage Form(s)</th>
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<tr>
<td>TCM</td>
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<th>13. Potency(ies)</th>
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<th>14. Chemical Name and Structure</th>
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<th>16. Comments:</th>
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An "Approvable" letter for S-035, dated 18 Dec 98, was sent to the firm requesting submission of Final Printed Labeling for a revised Package Insert (PI). The amendment is in response to this letter. The actual changes are highlighted or struck out, as appropriate.

**DESCRIPTION**

ZESTRIL is supplied as 2.5 mg, 5 mg, 10 mg, 20 mg, 30 mg, and 40 mg tablets for oral administration.

<table>
<thead>
<tr>
<th>17. Conclusions and Recommendations:</th>
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APPROVAL is recommended.

<table>
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<th>18.</th>
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<tbody>
<tr>
<td>Name James H. Short</td>
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**REVIEWS**

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**Distribution:**

- [ ] Original Jacket
- [ ] Reviewer
- [ ] Division File
- [ ] CSO
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<tr>
<td>Zenera Pharmaceuticals</td>
<td>S-035 15 Oct 98</td>
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<td>Wilmington, DE 19897</td>
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<td>1-[(N²-[(S)-1-Carboxy-3-phenylpropyl]-L-lysyl]-L-proline dihydrate</td>
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<td>The applicant certifies that a copy of this supplement has been submitted to SJN-DO.</td>
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<th>18. REVIEWER</th>
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<tbody>
<tr>
<td>Name: James H. Short</td>
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<td>Distribution: ✓ Original Jacket</td>
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<td>Date-Completed: 20 Nov 98</td>
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jhs/11/9/98/N19-777.S35

30-98
RHPM Review of Labeling

NDA: 19-777/SCM-035 Zestril (lisinopril) 2.5, 5, 10, 20, and 40 mg Tablets

Date of submissions: December 22, 1998 and January 8, 1999

Date of receipt: December 23, 1998 and January 11, 1998

Applicant: Zeneca Pharmaceuticals

Background: We issued an approvable letter dated December 18, 1998, for this manufacturing supplement to provide for a new 30 mg tablet strength of Zestril (lisinopril) Tablets. The letter requested that the firm submit final printed labeling identical to the package insert and immediate container and carton labels included in the October 15, 1998 submission, with one exception: a correction of the zip code at the end of the package insert.

Review:
Zeneca notes in the cover letter to the December 22, 1998 submission that the 30 mg tablet will be marketed prior to the production and marketing of the revised 2.5 mg tablet that was approved in supplement 034, so the submitted package insert does not include information on the revised 2.5 mg tablet. The labeling will be updated to include information on the revised 2.5 mg tablet when it is marketed, and the labeling change will be reported in the next annual report.

The submitted final printed labeling has been revised as follows:

DESCRIPTION: The third and fifth paragraphs have been revised to include “30 mg.”

HOW SUPPLIED: The following has been added:
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.

At the end of the package insert,
“Manufactured by: IPR Pharmaceuticals Inc.
Distributed by:
Zeneca Pharmaceuticals
A Business Unit of Zeneca Inc.
Wilmington, DE 19850-5437”

has been revised to:
“ZENEECA
Manufactured for:
Zeneca Pharmaceuticals
A Business Unit of Zeneca Inc.
Wilmington, Delaware 19850-5437”
By: IPR Pharmaceuticals, Carolina, Puerto Rico

I spoke to Mr. Robert Orzolek on January 5, 1999, and he agreed submit final printed immediate container labels as soon as possible. The container labels arrived on January 11, 1999. They appear to be adequate; the chemist will also review them.

Recommendation: I will prepare an approval letter for this supplement. This supplement falls under 21 CFR 314.70 (b)(3) Supplements requiring FDA approval before the change is made.

Kathleen F. Bongiovanni 1-12-99

cc: 19-777/S-035
     HFD-110
     HFD-110/KBongiovanni
     HFD-110/SBenton
     HFD-810/KSrinivasichar/JShort
     HF-2/MedWatch

kb/1/5/99; 1/12/99.
RHPM Review of Labeling

NDA: 19-777/SCM-035 Zestril (lisinopril)
2.5, 5, 10, 20, and 40 mg Tablets

Date of submission: October 15, 1998
Date of receipt: October 15, 1998
Applicant: Zeneca Pharmaceuticals

Background: Zeneca has submitted this manufacturing supplement to provide for a new 30 mg tablet strength of Zestril (lisinopril) Tablets. James Short, Ph.D., found the supplement approvable in his chemistry review dated November 30, 1998.

Review: The submitted draft labeling has been revised as follows:

DESCRIPTION: The third and fifth paragraphs have been revised to include “30 mg.”

HOW SUPPLIED: The following has been added:

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.

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has been revised to:

“ZENeca
Manufactured for:
Zeneca Pharmaceuticals
A Business Unit of Zeneca Inc.
Wilminton, Delaware 19850-5487
By: IPR Pharmaceuticals, Carolina, Puerto Rico”

I called Robert Orzolek at Zeneca on December 16, 1998, and asked him whether the zip code at the end of the package insert is correct. He said that it is not, and it should read “19850-5437.”
**Recommendation:** I will prepare an approvable letter for this supplement, asking for final printed labeling identical to the draft included in the October 15, 1998 submission, except with the corrected zip code as noted above. This supplement falls under 21 CFR 314.70 (b)(3) Supplements requiring FDA approval before the change is made.

Kathleen F. Bongiovanni  
12/16/98

cc: 19-777/S-035  
HFD-110  
HFD-110/KBongiovanni  
HFD-110/SBenton  
HFD-810/KSrinivasichar/JShort  
HF-2/MedWatch  
kb/12/3/98; 12/16/98.