# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPLICATION NUMBER: NDA 19777/S17

## CORRESPONDENCE

19-777
19.1
S-017

NDA 19-777/S-017

APR 1 1993

Zeneca Inc.
Attention: Robert Castor
Wilmington, DE 19897

Dear Mr. Castor:

Please refer to your February 12, 1993 supplemental new drug application submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Zestril (lisinopril) Tablets.

The supplemental application provides for manufacture and packaging of Zestril Tablets by IPR Pharmaceuticals, Inc.

We have completed our review and find the information presented is inadequate and the supplemental application is not approvable under section 505(b)(1) of the Act and 21 CFR 314.125(b). The deficiencies may be summarized as follows:

1. Please provide a copy of an executed batch record for manufacture of the 20 mg tablets.

2. Please provide CofAs for all lots of Zestril tablets manufactured by IPR.

3. Please include a commitment to place the first three production lots of the 10 and 20 mg tablets packaged in HDPE bottles into your stability program.

4. Please recommend to IPR that their EA be included in their DMF.

Within 10 days after the date of this letter, you are required to amend this supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. In the absence of any such action FDA may withdraw this supplemental application.

Sincerely yours,

4-1-93

Robert J. Wolters, Ph.D.
Supervisory Chemist
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

1800 Concord Pike
Wilmington
Delaware 19897 USA

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NDA/SUPPL AMEND/SUPP

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S-017

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Robert J. Wolters, Ph.D.
Supervisory Chemist
Division of Cardio-Renal
Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
HFD No. 110, Room No. 16B-30
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Wolters:

Re: ZESTRIL® (lisinopril) Tablets
NDA 19-777/S-017

The purpose of this submission is to respond to your letter of April 1, 1993 concerning the manufacture and packaging of ZESTRIL® (lisinopril) Tablets by IPR Pharmaceuticals, Inc.

1. PLEASE PROVIDE A COPY OF AN EXECUTED BATCH RECORD FOR MANUFACTURE OF THE 20 MG TABLETS.

   Attached as Exhibit 1 is an executed batch record by the manufacturer of SA03V, ZESTRIL Tablets 20 mg.

2. PLEASE PROVIDE COFAs FOR ALL LOTS OF ZESTRIL TABLETS MANUFACTURED BY IPR.

   Attached as Exhibit 2 are the Certificates of Analysis for all lots of ZESTRIL Tablets manufactured by IPR:

   ZESTRIL Tablets 5 mg - PA02V, PA03V, PA04A
   ZESTRIL Tablets 10 mg - RA01V, RA02V, RA03V
   ZESTRIL Tablets 20 mg - SA01V, SA02V, SA03V
   ZESTRIL Tablets 40 mg - TA01V, TA02V, TA03V

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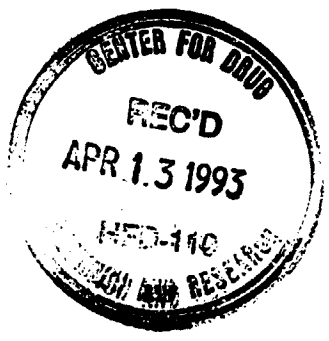

3. PLEASE INCLUDE A COMMITMENT TO PLACE THE FIRST THREE PRODUCTION LOTS OF THE 10 AND 20 MG TABLETS PACKAGED IN HDPE BOTTLES IN YOUR STABILITY PROGRAM.

The Sponsor commits to place the first 3 commercial production lots of ZESTRIL Tablets 10 mg and 20 mg in HDPE bottles in a commercial stability program. Results of the stability testing program will be submitted in the next periodic report. Any lots which fall outside of the approved specifications for the drug product may be withdrawn from the market. Variations that do not affect the safety and efficacy of the product will be promptly reported to the Agency and discussed between the Sponsor and the Agency.

4. PLEASE RECOMMEND TO IPR THAT THEIR EA BE INCLUDED IN THEIR DMF.

IPR has updated their Drug Master File on April 7, 1993 to include their Environmental Assessment of their Carolina Puerto Rico site. For your convenience, a copy of the updating letter is attached as Exhibit 3.

Sincerely,

Robert Castor
Manager
Technical Regulatory Affairs and Compliance
Drug Regulatory Affairs Department
(302) 886-2594
(302) 886-2822 (fax)

RC/jr
Enclosures

Desk Copy: Dr. James H. Short, HFD No. 110, Room No. 16B-30

ZENECA

NDA NO. 19-777 REF. NO. S-017

NDA SUPPL FOR - SCM

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Delaware 19897

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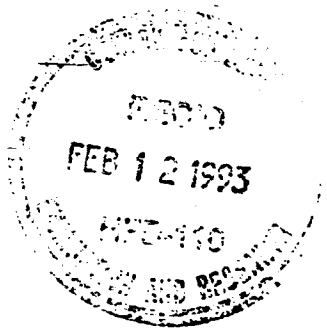
FEB 12 1993




Gentlemen:

Re: ZESTRIL® (lisinopril) Tablets
NDA 19-777

The purpose of the Supplemental NDA is to provide for an alternate manufacturer and packager for ZESTRIL® (lisinopril) Tablets. The site will be the Sponsor's subsidiary:

IPR Pharmaceuticals, Inc.
La Ceramica Industrial Park
Sabana Gardens
Carolina, PR 00984-1967

The 5, 10, 20 and 40 mg dosage strengths of ZESTRIL Tablets will be manufactured at this alternate site.

All pertinent information relating to the site in Puerto Rico is contained in the IPR Pharmaceuticals, Inc. Drug Master File (DMF A copy of a letter from IPR to the Agency authorizing the Agency to access this DMF on behalf of the Sponsor is enclosed as Exhibit 1.

ZESTRIL Tablets contain only one active ingredient, namely, lisinopril. Full details of its manufacture, characterization, control and stability have been previously included as referenced in the Sponsor's approved NDA 19-777. The preparation, specifications and control methods for the drug substance and excipients to be used at the alternate site are unchanged from those contained in NDA 19-777.

The qualitative and quantitative formulations for all dosage strengths to be manufactured at the alternate site are identical to those contained in the Sponsor's approved NDA 19-777. For your convenience, these formulations are enclosed as Exhibit 2.

The manufacturing process to be employed at the alternate site is essentially identical to that currently in use at the approved Newark, Delaware site, with a few minor exceptions. These exceptions are noted in the flow chart and tabular process comparisons enclosed as Exhibit 3.

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Exhibit 4 contains a brief outline of the manufacturing directions and a schematic flow chart of the process.

Comparative dissolution studies conducted on batches of each dosage strength of ZESTRIL Tablets manufactured at each site indicate no significant differences. The results of these studies are contained in Exhibit 5 enclosed.

The specifications and test methods to be used by IPR for all excipients entering into the manufacture of the drug product, and for the drug product itself, are compendial and are unchanged from those contained in the Sponsor's approved NDA.

Executed batch records for the ZESTRIL Tablet 5 mg dosage strength (which shares a common granulation with the ZESTRIL Tablet 10 mg dosage strength) and the ZESTRIL Tablet 40 mg strength are contained in Exhibit 6.

The packaging process implemented at IPR is a typical pharmaceutical packaging operation using state-of-the-art equipment which is described in Section F of the IPR Drug Master File, DMF

Packaging components to be used at IPR are identical to those used at the Sponsor's Newark, Delaware site. In addition, IPR will utilize HDPE bottles manufactured by A letter of authorization to access Drug Master File on behalf of IPR Pharmaceuticals, Inc. has been forwarded to the Agency. A copy of this letter and a letter of commitment and guarantee are enclosed as Exhibit 7.

HDPE bottles supplied by were submitted to the United States Testing Company Inc. for equivalency testing in accordance with USP XXII, Sections 661 and 671, and were found to be in compliance with the USP requirements. A copy of the test report is enclosed as Exhibit 8.

IPR will package all dosage strengths manufactured at that site in HDPE bottles and Hospital Unit Dose packs with the exception of the 40 mg dosage strength which will be packaged in HDPE bottles only.

Comparative stability studies were conducted on 3 lots of IPR-manufactured tablets and 1 lot of Newark-manufactured tablets in the following strengths and packages:

5 mg and 40 mg tablets in HDPE containers
5 mg, 10 mg and 20 mg tablets in Hospital Unit Dose blisters

The comparative study testing protocols are enclosed as Exhibit 9.

These studies indicate no significant differences between ZESTRIL Tablets manufactured at IPR and at the Newark, Delaware site. The results of these studies are reported in Exhibit 10.

Also enclosed as Exhibit 11 are the ongoing stability protocols, including the proposed post-approval (commercial) stability protocols, which will be observed at IPR.

The results of the stability testing of the IPR and Newark batches conducted at room temperature conditions (30°C, 50% RH) are enclosed as Exhibit 12.

Draft copies of the labeling to be used for ZESTRIL Tablets manufactured at the alternate site are enclosed as Exhibit 13.

This draft labeling does not include the storage statement "Store at controlled room temperature 15°C to 30°C (59°F to 86°F)" as requested by the Agency in its letter to the Sponsor dated January 15, 1993.

The Sponsor hereby commits to include the storage statement in its final printed labeling prior to distribution of the product to the marketplace.

Environmental Assessment information for the manufacturing of ZESTRIL Tablets at IPR Pharmaceuticals, Inc., Puerto Rico, is enclosed as Exhibit 14.

If you should require any additional information or clarification, please do not hesitate to contact me.

Sincerely,

Robert Castor
Manager
Technical Regulatory Affairs and Compliance
Drug Regulatory Affairs Department
(302) 886-2594

RC/mjb
Enclosures