CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: NDA 19777/S34

APPROVAL LETTER

NDA 19-777/S-034

NOV - 6 1998

Zeneca Pharmaceuticals
Attention: Mr. Norbert R. Ealer
P.O. Box 15437
Wilmington, DE 19850-5437

Dear Mr. Ealer:

Please refer to your June 24, 1998 supplemental new drug application 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 amendment dated August 7, 1998.

The supplemental application provides for an alternate manufacturing and packaging site, in addition to a change in tablet shape, for 2.5 mg Zestril tablets. The alternate site is IPR Pharmaceuticals located at Sabana Gardens Industrial park, Carolina, PR.

We have completed the review of this supplemental application and it is approved.

We bring to your attention that, in conformance with Agency policy, you may ship the 2.5 mg tablets labeled with the words "New Tablet Shape" for no more than six months after approval.

If you manufacture the 2.5 mg tablet at Newark in the future, it must have the round shape so that it conforms with the description in the HOW SUPPLIED section of the Package Insert.

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

Sincerely yours,

/S/ 11-6-98

Kasturi Srinivasachar, Ph.D.
Chemistry Team Leader, DNDC I
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: NDA 19777/S34

CHEMISTRY REVIEW(S)

OCT 30 1998

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) SCM-034 24 Jun 98
5. Drug Name Zestril	6. Nonproprietary Name Lisinopril	7. Amendments & Other (reports, etc) - Dates Amendment 7 Aug 98
8. Supplement Provides For: IPR Pharmaceuticals, Inc., Carolina, PR, as an alternate site for manufacture of the 2.5 mg tablet.		
9. Pharmacological Category Antihypertensive	10. How Dispensed ☒ 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		15. Records/Reports Current ☒ Yes ☐ No Reviewed ☒ Yes ☐ No

16. Comments:

The firm requests approval of the following facility as an alternate manufacturing site for the 2.5 mg tablets. This facility has already been approved for manufacture of the other strengths (S-017, 26 May 93).

IPR Pharmaceuticals, Inc.
Sabena Gardens Industrial Park
Carolina, PR 00984-1967

An EER, dated 26 Jun 98, was sent to HFD-324 *via* the EES system. An "Acceptable" response, dated 13 Jul 98, was received on 4 Sep 98. A copy is attached.

17. Conclusions and Recommendations:

APPROVAL is recommended.

18.

Name James H. Short

REVIEWED /S/

Date Completed 22 Sep 98

Distribution: ☒ Original Jacket ☒ Reviewer ☒ Division File ☒ CSO

jhs/9/8/98/N19-777.S34

K. Swindler 10-22-98

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19777/S34

CORRESPONDENCE

COPY 1
ORIGINAL

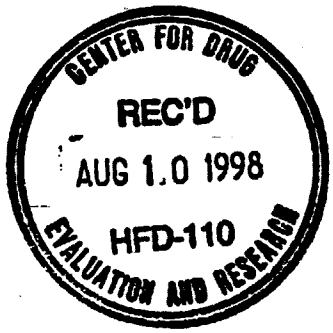
ZENECA
Pharmaceuticals
A Business Unit of Zeneca Inc.

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

SENT VIA UNITED PARCEL SERVICE

AUG 07 1998

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
1451 Rockville Pike
Rockville, MD 20852



NDA APPROVED
SCM-034
(BC)

Dear Dr. Lipicky:

Re: ZESTRIL® (lisinopril) Tablets 2.5 mg
NDA 19-777

Reference is made to the supplemental New Drug Application Number S-034, submitted on June 24, 1998. Supplement Number S-034 provides data in support of:

- An alternate site for manufacturing and packaging of ZESTRIL® (lisinopril) 2.5 mg Tablets
- A change in tablet shape

The data presented here in Attachment 1 is submitted to satisfy a commitment made by the Sponsor to provide three months' stability data for the two lots of ZESTRIL 2.5 mg Tablets manufactured at IPR. The product will be packed in 100 count bottles only.

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

Sincerely,

Norbert R. Ealer
Regulatory Consultant
Chemistry, Manufacturing and Control Group
Drug Regulatory Affairs Department
(302) 886-7633
(302) 886-2822 (fax)

NRE/jr
Enclosure

Desk Copy: Dr. James H. Short, HFD No. 110

ORIGINAL

P:\EALER\FDA\ZESTRIL\19777 S-034 ALTERNATE SITE ETC.DOC

ORIGINAL

ZENECA
Pharmaceuticals
A Business Unit of Zeneca Inc.

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

COPY 1

JUN 24 1998

SENT VIA UNITED PARCEL SERVICE

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
1451 Rockville Pike
Rockville, MD 20852

NDA NO. 19-777 SUPPL. NO. 034
NDA SUBMISSION SCM

CENTER FOR DRUG
REC'D
JUN 26 1998
HFD-110
EVALUATION AND RESEARCH

Dear Dr. Lipicky:

Re: ZESTRIL® (lisinopril) Tablets 2.5 mg
NDA 19-777

The purpose of this supplemental New Drug Application is to provide the Agency data to support:

- An alternate site for manufacturing and packaging of ZESTRIL® (lisinopril) 2.5 mg Tablets:

  The site will be IPR Pharmaceuticals, Inc. (IPR) located at Sabana Gardens Industrial Park, Carolina, Puerto Rico 00984-1967.

- Change in the tablet shape:

  The current description is "Oval, white, biconvex, uncoated tablet embossed 'ZESTRIL' and '2½' on one face, opposite face embossed '135'."

  The proposed description is "Round, white, biconvex, uncoated tablet embossed 'ZESTRIL' and '2½' on one face, opposite face embossed '135'."

ZESTRIL 2.5 mg Tablets will be packed at IPR in bulk drums and 100 count bottles.

ORIGINAL

The facility has a satisfactory GMP Status based on an inspection performed from **February 12, 1997 to March 27, 1997**. **Appendix 1** contains IPR's GMP Compliance Certification.

ZESTRIL 2.5 mg Tablets contain one active ingredient, namely, lisinopril. It is unchanged from the Sponsor's approved tablets NDA.

The preparation, specifications and test methods to be used by IPR for the drug substance, and all excipients entering into the manufacture of the drug product and for the drug product itself, are unchanged from those contained in the Sponsor's approved NDA, with the exception of the description as noted above.

All IPR manufactured ZESTRIL Tablets used in the comparative dissolution and stability studies referenced below have used lisinopril manufactured at the Sponsor's approved Guayama, Puerto Rico site. They are in the new round tablet shape.

The Newark, Delaware manufactured batches reported in this submission used lisinopril manufactured at the Sponsor's approved Macclesfield, UK site.

The master formula, including the qualitative and quantitative formulation for the 2.5 mg tablets dosage strength to be manufactured at IPR, is unchanged from the current approved NDA. For your convenience, the master formula is enclosed as **Appendix 2.**

The manufacturing process to be employed at the IPR site is essentially the same as that currently in use at the Sponsor's approved Newark, Delaware site, with a few minor exceptions. These process changes were noted and approved in the sNDA 19-777, S-017, dated February 12, 1993 and approved on May 26, 1993.

These exceptions are noted in the flow chart and tabular process comparisons enclosed as **Appendix 3**. The Manufacturing Order is contained in **Appendix 4**. An executed batch record for ZESTRIL 2.5 mg Tablets is contained in **Appendix 5.**

Appendix 6 contains three (3) Certificates of Analysis for ZESTRIL 2.5 mg Tablets, Lot Numbers CAA030, CAA040 and 0335Y.

Comparative dissolution studies were conducted on one batch of ZESTRIL 2.5 mg Tablets manufactured at Newark, Delaware (Lot Number 0335Y), and two (2) batches of ZESTRIL 2.5 mg Tablets manufactured at IPR (Lot Numbers CAA030 and CAA040). The dissolution comparative study protocol and report are enclosed as **Appendix 7**. The results of these studies indicate no significant difference between the ZESTRIL Tablets manufactured at IPR and at the Newark, Delaware site.

Appendix 8 contains engineering drawings of the new shape tablet.

The Sponsor commits to provide three months' stability data for the two lots of ZESTRIL 2.5 mg Tablets manufactured at IPR and packaged in the bulk drum, and 100 count bottle placed under accelerated conditions (40°C/75%RH) to the Division of Cardio-Renal Drug Products as soon as it is available.

Commercial stability testing (25°C/60% RH) will be conducted on the first commercial batch. The results from this stability testing will be submitted in the Annual Report, or as specified by the FDA.

Results from these stability evaluations will be reviewed against the requirements of this application. Product which does not meet approved specifications will be withdrawn from the market. If there is evidence that the deviation is a single occurrence that does not affect the safety and efficacy of the drug product, we will promptly discuss the deviation with the Division of Cardio-Renal Drug Products, provide justification for the continued distribution of the batch, and file a report as required under 21 CFR 314.81 (b) (1) (ii).

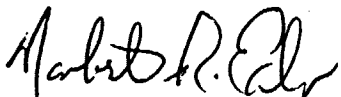
Draft copies of the labeling to be used for ZESTRIL 2.5 mg Tablets manufactured at the alternate site are enclosed as **Appendix 9**.

Environmental Assessment information for the manufacture of ZESTRIL 2.5 mg Tablets at IPR Pharmaceuticals, Inc., Puerto Rico, is enclosed as **Appendix 10**.

In accordance with Section 314 of Title 21 of the Code of Federal Regulations [21 CFR 314.50 (k) (3)], Zeneca Inc. certifies that a copy of this supplemental NDA has been submitted to the FDA San Juan District Office and has been designated as the Field Copy.

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

Sincerely,



Norbert R. Ealer
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NRE/jr
Enclosures

Desk Copy: Dr. James H. Short, HFD No. 110