

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: NDA 19777/S1

APPROVAL LETTER

NDA 19-777/S-001

JUN 30 1988

Stuart Pharmaceuticals
ICI Americas Inc.
Attention: Mr. Richard J. Pierce
Wilmington, DE 19897

Dear Mr. Pierce:

We acknowledge the receipt on June 16, 1988 of your June 8, 1988 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 the following changes in the container labels:

The company name "Stuart" has been added to follow the generic name.

The product trademark designation used is "TM" rather than "R."

We have completed the review of this supplemental application and it is approved. Our letter of May 19, 1988 detailed the conditions relating to the approval of this application.

At the time of the next printing, please separate lisinopril and Stuart with a comma or place Stuart in parentheses. Also, please include the statement "Protect from moisture, freezing and excessive heat."

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

Should you have any questions, please contact:

Ms. Kathleen Bongiovanni
Consumer Safety Officer
Telephone: (301) 443-4730

Sincerely yours,

cc: Original NDA
HFD-110
HFD-110/CSO
HFD-80/DDIR
HFD-232 (with labeling)
HFD-110/KBongiovanni
sb/6/17/88;6/24/88;6/27/88/1013S
R/D: JShort/6/20/88;6/24/88
RWolters/6/20/88
GBuehler for NAM

ISI
6-27-88

ISI 6/30/88

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

APPROVAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19777/S1

FINAL PRINTED LABELING

Labeling: Original
NDA No: 19-7770 Re'd. Jun 16, 1982
Reviewed by: KS 6-27-88

WARNING: As with all medications, keep out of the reach of children. Dispense in well-closed container.

NDC 0289-0130-10
ZESTRIL™
LISINOPRIL STUART
20 mg TABLETS

CAUTION: Federal law prohibits dispensing without prescription. 100 TABLETS

USUAL DOSAGE: See accompanying Professional Information Brochure.

APPROVED

JUN 30 1988

0289-01

STUART PHARMACEUTICALS | Div. of ICI Americas Inc. | KILGORE, MISSOURI 64588

LIT
EXP

ZESTRIL™

LISINOPRIL STUART

ZESTRIL™

LISINOPRIL STUART

New patient starter sample
for use in hypertension

10 MG TABLETS

WARNING: As with all medications, keep out of the reach of children. Dispense in well-closed container.

NDC 0289-0130-10
ZESTRIL™
LISINOPRIL STUART
5 mg TABLETS

CAUTION: Federal law prohibits dispensing without prescription. 100 TABLETS

USUAL DOSAGE: See accompanying Professional Information Brochure.

0289-01

STUART PHARMACEUTICALS | Div. of ICI Americas Inc. | KILGORE, MISSOURI 64588

LIT
EXP

PROFESSIONAL SAMPLE—NOT TO BE SOLD

DOSAGE: One tablet daily or as directed by physician

CAUTION: Federal law prohibits dispensing without prescription

WARNING: As with all medications, keep out of reach of children.

30113-00

STUART PHARMACEUTICALS | Div. of ICI Americas Inc. | KILGORE, MISSOURI 64588

ONE TABLET A DAY

ZESTRIL™

LISINOPRIL STUART

Labeling: Original
NDA No: 19-777 No. 6 June 6,
Reviewed by: Ka 6-2788

WARNING: As with all
medications, keep out
of the reach of children.
Dispense in well-closed
container.

100-0000-0001-00

ZESTRIL™
LISINOPRIL STUART

10 mg TABLETS

Cautions: Federal law prohibits dispensing
without prescription.

100 TABLETS

UNITED STATES PATENT AND TRADEMARK OFFICE
REGISTERED, CLASS 283, 287

LEGAL NOTICE:
See accompanying
Prescription
Information Statement.

LOT
EXP

APPROVED

4 new
patient starter samples
for use in hypertension

ZESTRIL™
LISINOPRIL STUART

ZESTRIL™
LISINOPRIL STUART

10 MG TABLETS

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CHEMISTRY REVIEW(S)

JUN 30 1988

CHEMIST'S REVIEW <small>(If necessary, continue any item on 8" x 10 1/2" paper. Key continuation to item by number.)</small>		1. ORGANIZATION HFD-110	2. NDA NUMBER 19-777
3. NAME AND ADDRESS OF APPLICANT (City and State) Stuart Pharmaceuticals Wilmington, DE 19897		4. AF NUMBER 7-612	
6. NAME OF DRUG Zestril		7. NONPROPRIETARY NAME Lisinopril	5. SUPPLEMENT (S) NUMBER(S) DATE(S) S001 6/9/88
8. SUPPLEMENT(S) PROVIDES FOR: revised FPL.		9. AMENDMENTS AND OTHER (Reports, etc.) DATES	
10. PHARMACOLOGICAL CATEGORY Antihypertensive	11. HOW DISPENSED <input checked="" type="checkbox"/> RX <input type="checkbox"/> OTC	12. RELATED IND/NDA/DMF(S) NDA 19-558 (lisinopril, Merck)	
13. DOSAGE FORM (S) TCM	14. POTENCY (See) 5, 10 and 20 mg	16. RECORDS AND REPORTS CURRENT <input type="checkbox"/> YES <input type="checkbox"/> NO REVIEWED <input type="checkbox"/> YES <input type="checkbox"/> NO	
15. CHEMICAL NAME AND STRUCTURE see Review #1		17. COMMENTS The labels provided in this supplement are satisfactory from a technical standpoint, except that the firm name following the generic name should be in parenthesis or preceded by a comma. The following statement should be included, "Protect from moisture, freezing and excessive heat."	
18. CONCLUSIONS AND RECOMMENDATIONS The following information should be conveyed to the applicant: "At the time of the next printing please separate "lisinopril" and "Stuart" by a comma, or place "Stuart" in parenthesis. Also at the time of the next printing please include the statement "Protect from moisture, freezing and excessive heat." <i>Handwritten: 6/29/88</i>			
19. REVIEWER NAME: James H. Short <i>JS</i> DATE COMPLETED: JUN 29 1988			
DISTRIBUTION <input checked="" type="checkbox"/> ORIGINAL JACKET <input checked="" type="checkbox"/> REVIEWER <input type="checkbox"/> DIVISION FILE			

CENTER FOR DRUG EVALUATION AND RESEARCH

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**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

MAR 19 1998

CLINICAL PHARMACOLOGY/BIPHARMACEUTICS REVIEW

Meeting Summary

IND/NDA# 19,777
Zestril (Lisinopril)

Reviewer: Nakissa Sadrieh, Ph.D.

Drug Class: ACE inhibitor

Submission date: 2/16/1998
Meeting Date: 3/18/93

Indication: Renal and Retinal complications of Diabetes Mellitus.

Purpose/Background: Zeneca is currently marketing Zestril (lisinopril) for the treatment of hypertension, adjunctive therapy in the management of heart failure and the treatment of hemodynamically stable patients within 24 hours of an acute MI. the sponsor wishes to add two additional indications based on data from 2 clinical trials (306 and 298). The additional two indications are 1) to treat incipient nephropathy in normotensive IDDM and hypertensive NIDDM patients and 2) for reducing the risk of progression of retinopathy in normotensive IDDM patients. The sponsor wishes to ask the division 2 questions: 1) Would the efficacy and safety data from the 2 reported clinical trials (306 and 298) support the submission and approval of an supplemental application for the above-stated indications? 2) If the data do not support the inclusion of these additional indications in the Indication and Usage section of the package insert, then the sponsor wishes to know whether the data could be included in the clinical pharmacology section.

Biopharm/Clinical Pharmacology issues:

No biopharm/clinical pharmacology issues were identified.

Comments:

Recommendations:

No biopharm/clinical pharmacology issues were identified therefore no recommendations are warranted from the clinical PK perspective.

FT: Patrick Marroum, Ph.D.

IS/

IS/ Nakissa Sadrieh, Ph.D.

3/19/98

CC: N 19-777; HFD-110 (Bongiovani); HFD-860 (Sadrieh; Marroum); CDER document room

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19777/S1

CORRESPONDENCE

ZENECA

Pharmaceuticals

A Business Unit of Zeneca Inc.

ORIGINAL

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

SUPPL NEW CORRESP

(SNC)
(B001)
CUT 1

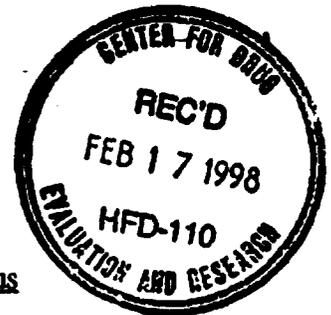
SENT VIA FEDERAL EXPRESS

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

FEB 16 1998

Dear Dr. Lipicky:

Re: ZESTRIL® (lisinopril) Tablets
NDA 19-777
Request for Meeting/
Briefing Document - Renal and Retinal Complications of Diabetes Mellitus



Enclosed is a briefing document which provides background information for the use of ZESTRIL® (lisinopril) Tablets in the treatment of the renal and retinal complications of diabetes mellitus. ZESTRIL is currently indicated for the treatment of hypertension, adjunctive therapy in the management of heart failure, and the treatment of hemodynamically stable patients within 24 hours of an acute myocardial infarction.

Zeneca wishes to receive comment from the Division of Cardio-Renal Drug Products on a proposed indication for the use of ZESTRIL to treat incipient nephropathy in normotensive IDDM and hypertensive NIDDM patients and for reducing the risk of progression of retinopathy in normotensive IDDM patients. The proposed indication is supported by the results of two clinical studies, Trial 306 (also known as EUCLID) which was independently conducted by the and Trial 298 (also known as BRILLIANT) which was conducted by Zeneca Pharmaceuticals in Europe.

ORIGINAL

Trial 306 included 530 normotensive IDDM patients and Trial 298 included 335 hypertensive NIDDM patients. In both trials, urinary albumin excretion rate was significantly reduced by lisinopril therapy. Additionally, in a subset of 354 patients in Trial 306, lisinopril significantly reduced the risk of progression of retinopathy. The results of these two clinical studies are described in detail in the enclosed briefing document. Accordingly, Zeneca requests comment from the Agency regarding the potential for obtaining regulatory clearance for the proposed indication for ZESTRIL based on data from Trial 306 and Trial 298.

We appreciate the Division's busy schedule, but request a two hour meeting at the earliest possible date, preferably before March 24, 1998. We anticipate that the FDA will review the information and provide feedback prior to the proposed meeting in order to focus the discussion and facilitate a productive meeting. Twelve review copies of the briefing document are included with this submission.

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

Sincerely,



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

RJO/lmc

Desk Copy: Ms. Kathleen Bongiovanni, HFD No. H11, Room No. 5023



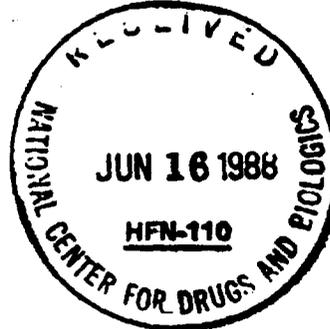
ICI Pharmaceuticals Group

COPY NDA 19-777 SUPPL FOR *Labeling Revision*
with ITL ICI Pharma
Stuart Pharmaceuticals

**CERTIFIED MAIL
RETURN RECEIPT REQUESTED**

June 8, 1988

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



Dear Dr. Wolters:

**Re: SPECIAL SUPPLEMENT - CHANGES BEING EFFECTED
ZESTRIL® (lisinopril)
NDA 19-777**

Confirming our telephone conversation of June 6, 1988, I take this opportunity to submit alternate product labels to the previously approved labeling submitted May 16, 1988 for the subject NDA.

This labeling differs from that previously submitted in that the company name "Stuart" has been added to follow the generic name, and the product trademark designation is "SM" rather than "SM". These labels were previously used for this product on a agreed to limited basis at the time of product approval under Merck Sharp & Dohme Research Laboratories' NDA 19-558. We agreed to temporarily discontinue the use of the company name in this manner until our own NDA 19-777 was approved. With the May 19, 1988 approval of our NDA, we are now returning to the attached labeling which employs the company name in this manner.

As agreed in our telephone conversation, we are implementing the use of this labeling immediately. We have enclosed twelve copies of final printed labeling. If you have any questions on this supplement, please do not hesitate to contact me.

Sincerely,

Richard J. Pierce
Assistant Director
Technical Regulatory Affairs and Compliance
Drug Regulatory Affairs Department
(302) 575-2196

RJP/cmh
Enclosure

ORIGINAL