CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19777/S8

CORRESPONDENCE

MAR 21 1990

NDA 19-777/S-008

ICI Pharmaceuticals Group
Attention: Robert Castor
Wilmington, DE 19897

Dear Mr. Castor:

Please refer to your February 14, 1990 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 an alternate pivotal intermediate for the production of lisinopril dihydrate.

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 an actual batch record for the preparation of the intermediate, and indicate the range of batch sizes which may be prepared.

2. Please include a description of the actual equipment used.

3. Please provide tests and specifications for all of the components used in the synthesis of the intermediate.

4. Please provide the details for the in-process controls.

5. Please ask to include an Environmental Assessment in their Drug Master File as mandated by 21 CFR 25.31a, even though this plant is outside the US. They should submit appropriate documentation stating that they comply with Japanese environmental laws and regulations. This documentation should be signed by officials of the Japanese government who are responsible for regulating emissions from manufacturing plants.

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.

cc:
Original NDA
HFD-110
HFD-110/CSO
HFD-80/DDIR
HFD-110/JShort/3/19/90
clb/3/21/90/2557C

NOT APPROVABLE

3/21/90

Sincerely yours,

3-21-90

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

NDA 19-777/S-008

SEP 18 1990

ICI Pharmaceuticals Group
Attention: Kevin McKenna, Ph.D.
Wilmington, DE 19897

Dear Dr. McKenna:

Please refer to your February 14, 1990 supplemental new drug application submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Zestril (lisinopril) Tablets.

We also acknowledge receipt of your amendment dated July 20, 1990.

The supplemental application provides for an alternate pivotal intermediate for the production of lisinopril dihydrate.

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

Please obtained from [ ] an Environmental Assessment in the format as required by 21 CFR 25.31a. It is also necessary for [ ] to provide documentation from the Japanese government verifying that they are in compliance with the appropriate regulations.

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,

9/18/90

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

cc:
Original NDA
HFD-110
HFD-110/CSO
HFD-713/GChi
HFD-80/DDIR
HFD-110/JShort/9/14/90
clb/9/17/90/3228C

9HS 9/18/90

NOT APPROVABLE

SCS008 DC

Pharmaceuticals Group

Stuart Pharmaceuticals/ICI Pharma

NDA SUPPL AMENDMENT

HAND DELIVERED

ICI Pharmaceuticals Group
Wilmington
Delaware 19897 USA

JUL 20 1990

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
Alternative Pivotal Intermediate

The purpose of this submission is to provide a response to the comments contained in your letter of March 21, 1990.

1. PLEASE PROVIDE AN ACTUAL BATCH RECORD FOR THE PREPARATION OF THE INTERMEDIATE, AND INDICATE THE RANGE OF BATCH SIZES WHICH MAY BE PREPARED.

   Attachment 1 contains an actual batch record from the pilot plant production of the intermediate and the range of batch sizes from the pilot plant production. Batch records from the full-scale production are unavailable because commercial production has not been started as of yet.

   The batch records from the pilot plant are written in Japanese. As agreed upon with Dr. James Short, a translation of the batch records will be provided, if he deems them indiscernible.

   Attachment 2 contains the differences in processes between the pilot plant and full-scale productions of the intermediate. The process used in the full-scale production will comply to that provided for in the Applicant's submission of February 14, 1990, and incorporates those changes set out in Attachment 2.

   The batch size of the full-scale production will be in the range of _____ Kg/batch.

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2. PLEASE INCLUDE A DESCRIPTION OF THE ACTUAL EQUIPMENT USED.

   Attachment 3 contains a description of the actual equipment used in the synthesis of the intermediate.

3. PLEASE PROVIDE TESTS AND SPECIFICATIONS FOR ALL THE COMPONENTS USED IN THE SYNTHESIS OF THE INTERMEDIATE.

   Attachment 4 contains the tests and specifications for all the components and the in-process controls used in the synthesis of the intermediate.

4. PLEASE PROVIDE THE DETAILS FOR THE IN-PROCESS CONTROLS.

   Please see item 3 above.

5. PLEASE ASK KANEGAFUCHI TO INCLUDE AN ENVIRONMENTAL ASSESSMENT.

   Attachment 5 contains an Environmental Assessment signed by the appropriate authority from which has been submitted for inclusion in their Drug Master File.

If you require any further information, please do not hesitate to contact me.

Sincerely,

Kevin McKenna

Kevin McKenna, Ph.D.
Senior Specialist
Technical Regulatory Affairs and Compliance
Drug Regulatory Affairs Department
(302) 886-2742

KM/rmw
Attachments

Desk Copy: Dr. James H. Short, HFD No. 110, Room No. 16-B19

NDA NO. .... REF. NO. ....
NDA SUPPL FOR ....

Pharmaceuticals Group

Stuart Pharmaceuticals/ICI Pharma

COPY 1

CENTER FOR DRUGS AND BIOLOGICS
REC'D
FEB 1 4 1990
HFN-11

ICI Pharmaceuticals Group
Wilmington
Delaware 19897 USA

HAND DELIVERED

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

FEB 1 4 1990

Gentlemen:

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

The purpose of this submission is to submit an alternate pivotal intermediate for the production of lisinopril dihydrate. This alternate intermediate is TFA-lisinopril ester manufactured for the Applicant by and may be used in place of TFA-lisinopril ester produced by

Attachment 1 is a letter from authorizing the Agency to refer to Drug Master File behalf of the Applicant.

Attachment 2 sets out the nomenclature and description including the structural formula for TFA-lisinopril ester.

Attachment 3 describes the synthetic route, process and components for the manufacture of TFA-lisinopril ester by

Attachment 4 provides the controls established for the intermediates used in the synthesis of TFA-lisinopril ester by

Attachment 5 outlines the impurities arising from the synthesis of TFA-lisinopril ester by

Attachment 6 sets out the specifications and test methods established for TFA-lisinopril ester.

ORIGINAL

Attachment 7 contains typical batch analyses of two lots of TFA-lisinopril ester manufactured by

Attachment 8 describes the synthetic route and process for the manufacture of lisinopril dihydrate using TFA-lisinopril ester manufactured by as the pivotal intermediate.

Attachment 9 provides:

a. batch analyses of lisinopril ester derived using starting materials contained in the approved synthetic process compared to produced TFA-lisinopril ester.
b. batch analyses of lisinopril crude derived using starting materials contained in the approved synthetic process compared to produced TFA-lisinopril ester.

Attachment 10 outlines the impurities arising from the synthesis of lisinopril dihydrate using TFA-lisinopril ester manufactured by as the pivotal intermediate.

The specifications and test methods for lisinopril dihydrate manufactured using TFA-lisinopril ester manufactured by as the pivotal intermediate are unchanged from those in place for the drug substance produced by the current approved synthetic route, except for the method for the determination of related impurities by gradient This method has been updated to resolve the cyclohexyl derivative impurity. The specifications and gradient impurity method are set out in Attachment 11.

Attachment 12 contains typical batch analyses of lisinopril dihydrate made using the currently approved TFA-lisinopril ester and also TFA-lisinopril ester as the pivotal intermediate.

The results of a 13-week stability study conducted on 1 batch of lisinopril dihydrate manufactured using TFA-lisinopril ester produced by as the pivotal intermediate is contained in Attachment 13.

Sincerely,

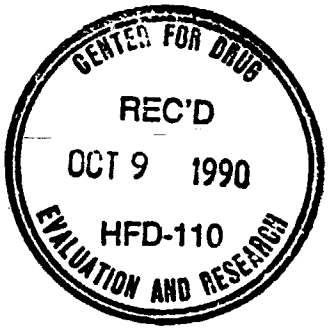
Robert Castor
Manager
Technical Regulatory Affairs and Compliance
Drug Regulatory Affairs Department
(302) 886-2594

RC/law
Attachment

NDA SUPPL AMENDMENT
SCS-008
(BC)

Pharmaceuticals Group

Stuart Pharmaceuticals/ICI Pharma



SENT VIA FEDERAL EXPRESS

ICI Pharmaceuticals Group
Wilmington
Delaware 19897 USA

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

OCT 8 1990

Dear Dr. Wolters:

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

This submission is in response to the comments contained in your September 18, 1990 letter regarding the applicant's supplemental New Drug Application providing for an alternative pivotal intermediate for the production of lisinopril dihydrate.

Please obtain from an Environmental Assessment in the format as required by 21 CFR 25.31a. It is also necessary for to provide documentation from the Japanese government verifying that they are in compliance with the appropriate regulations.

As discussed in our telephone conversation of October 1, 1990, please find attached an Environmental Assessment for in the format provided for in 21 CFR 25.31a. If deemed necessary, the applicant will provide additional information to support the attached Environmental Assessment.

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

Sincerely,

Kevin McKenna

Kevin McKenna, Ph.D.
Senior Specialist
Technical Regulatory Affairs and Compliance
Drug Regulatory Affairs Department
(302) 886-2742

KM/mjb
Attachment

ORIGINAL

Pharmaceuticals Group

Stuart Pharmaceuticals/ICI Pharma

COPY 1

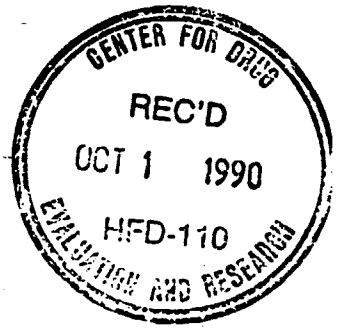
SUPPL NEW CORRES

ICI Pharmaceuticals Group

Wilmington
Delaware 19897 USA

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

SEP 26 1990



Dr. Robert J. Wolters
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-008

This letter is to acknowledge the receipt of your correspondence dated September 18, 1990, and to inform you that a response is being prepared addressing your comments on the subject supplemental new drug application.

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

Sincerely,

Kevin McKenna

Kevin McKenna, Ph.D.
Senior Specialist
Technical Regulatory Affairs and Compliance
Drug Regulatory Affairs Department
(302) 886-2742

KM/mjb

ORIGINAL