CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19777/S13

CORRESPONDENCE

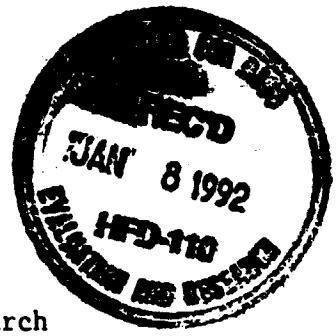
NDA NO: 19-777 SUPPL NO. 5-013

NDA SUPPL FOR SCS

Pharmaceuticals Group

Stuart Pharmaceuticals/ICI Pharma

COPY



HAND DELIVERED

ICI Pharmaceuticals Group
Wilmington
Delaware 19897 USA

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

JAN 8 1992

Gentlemen:

Re: ZESTRIL® (lisinopril) Tablets 5 mg
NDA 19-777

The purpose of this submission is to inform you that the sponsor is proposing to change the shape of its current ZESTRIL® (lisinopril) Tablet 5 mg to enable the sponsor to better distinguish the 5 and 10 mg dosage strengths of ZESTRIL Tablets. The shape of the ZESTRIL Tablet 5 mg will be changed from a round, biconvex, pink, bisected tablet to a capsule-shaped, biconvex, pink, bisected tablet.

The qualitative and quantitative formulations and manufacturing directions for the new capsule-shaped tablet are unchanged from those for the current round tablet. All test methods and specifications are also unchanged with the exception of the tablet description which will now be:

Appearance: Capsule-shaped, biconvex, pink, bisected, uncoated tablet, embossed on one side "ZESTRIL" and on the other side "130" and bisected.

The in-process guide for tablet hardness for the capsule-shaped tablet has been changed to a target of 6 Kp with a range of Kp, compared to a hardness target of 5 Kp with a range of Kp for the round tablet.

Attached as Exhibit 1 is a comparative dissolution study comparing the dissolution profile of the current and proposed tablet shapes. These profiles indicate no significant differences between the current and proposed tablet shapes.

ORIGINAL

If you require any further information, 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
Attachment

SUPPL NEW CORRES

SNC-013

Pharmaceuticals Group

Stuart Pharmaceuticals/ICI Pharma

SENT VIA FEDERAL EXPRESS

ICI Pharmaceuticals Group

Wilmington
Delaware 19897 USA

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 19 1992

Gentlemen:

Re: ZESTRIL® (lisinopril) Tablets 5 mg
NDA 19-777/S-013
Chemistry, Manufacturing and Control Information

The purpose of this submission is to provide a response to comments made by Dr. James H. Short during telephone conversations of February 5, 6, and 7, 1992 regarding the January 8, 1992 supplemental New Drug Application (SNDA). The subject SNDA provides for a change in the shape of the ZESTRIL® (lisinopril) Tablet 5 mg from a round, biconvex, pink, bisected tablet to a capsule-shaped, biconvex, pink, bisected tablet. To that end, the applicant offers the following points of clarification:

1. WHAT WAS THE RATIONALE BEHIND CHANGING THE TABLET HARDNESS SPECIFICATION? WAS IT TO KEEP THE TABLET COMPRESSION FORCE CONSTANT?

   During the development of the capsule-shaped tablet, the tablet hardness was varied to maintain a constant tablet compression force.

2. WHY WERE 2 DIFFERENT CAPSULE PUNCHES USED (ONE EMBOSSED WITH "ZESTRIL" AND THE OTHER EMBOSSED WITH "STUART"? WILL ONE CAPSULE PUNCH BE USED IN PREFERENCE TO THE OTHER?

   The applicant investigated the use of the "STUART" embossed capsule-shaped tablet punch as a contingency plan in the event of "picking and sticking" problems with the "ZESTRIL" embossed capsule-shaped tablet punches. To maintain the consistency of the ZESTRIL product line, the applicant will market only the ZESTRIL intagliated capsule-shaped tablets.

3. PLEASE CONFIRM THAT THE UNITS FOR THE ASSAY RESULT GIVEN IN TABLE I ARE "MG/TABLET" RATHER THAT MG/G OF GRANULATION."

   The Assay result listed in Table I is correct as given with the units of "mg/tablet". The result was generated using the Content Uniformity by Assay.

ORIGINAL

4. TABLE II PROVIDES INFORMATION/DATA ON TOOLING AND PHYSICAL TESTING ON 10 "LOTS" OF TABLETS (EG., 3 "LOTS" OF 6 MM ROUND TABLETS, 4 "LOTS" OF "ZESTRIL" INTAGLIATED TABLETS, AND 3 "LOTS" OF "STUART" INTAGLIATED TABLETS). TABLE III CONTAINS DISSOLUTION DATA ON ONLY 7 "LOTS" OF TABLETS. PLEASE PROVIDE CLARIFICATION ON WHAT RATIONALE WAS USED IN CHOOSING THE 7 OUT OF 10 "LOTS". IN ADDITION, PLEASE PROVIDE A MEANS OF CROSS-REFERENCING THE 7 "LOTS" USED TO GENERATE THE DISSOLUTION DATA GIVEN IN TABLES III THROUGH IX TO THE TOOLING AND PHYSICAL TESTING DATA GIVEN IN TABLE II.

   Dissolution data were collected on the 3 "lots" of 6 mm round tablets and the 4 "lots" of "ZESTRIL" intagliated capsule-shaped tablets.

   Attachment A contains a revised Table II in which the first "lot" of 6 mm round tablets manufactured using a compression force of ___lbs. is denoted as "lot" #1 in the table, and the remaining "lots" are numbered in ascending order with the "STUART" intagliated capsule-shaped tablets manufactured using a compression force of lbs. denoted as "lot" #10.

   Attachment B includes revised Tables III through IX in which the "lot" numbering system described in the preceding paragraph has been incorporated, thus allowing the data listed in Tables III through IX to be cross-referenced to that provided in Table II.

5. IN TABLES III THROUGH IX, UNITS OF TABLET HARDNESS ARE GIVEN FOR COMPRESSION FORCE. PLEASE CLARIFY THIS DISCREPANCY.

   The units of tablet hardness listed in Tables III through IX are correct. The compression force descriptor is incorrect, and should read "Targeted Tablet Hardness." The tablet hardness values listed in Tables III through IX have been revised to reflect those listed is Table II and represent observed tablet hardness.

   The Tables provided for in Attachment B had been corrected to provide the proper descriptor. The applicant apologizes for any inconveniences this error may have caused in the review process.

6. THE APPLICANT STATES IN THE EXPERIMENTAL SECTION OF THE SUBMISSION THAT FOUR PERMUTATIONS OF THE CAPSULE-SHAPED TOOLING WERE COMPARED WITH CURRENT ROUND PRODUCTION TOOLING. THE SUBMISSION CONTAINS DATA ON ONLY 2 PERMUTATIONS OF THE CAPSULE-SHAPED TOOLING. PLEASE CLARIFY THE DISCREPANCY.

   The applicant investigated only 2 permutations of the capsule-shaped tooling. The 4 x 8 mm capsule-shaped punches were obtained from ___. They are intagliated in the following combinations:
   (1) "ZESTRIL" embossed horizontally on the lower punch and "130" embossed perpendicular on the bisect of an upper punch; and
   (2) "STUART" embossed horizontally on the lower punch and "130" embossed parallel to a bisect on the upper punch.

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

Sincerely,

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

RC/KM/mjb

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