Application Number: NDA 19777/S4

APPROVAL LETTER
ICl Pharmaceuticals Group
Attention: Mr. William A. Best
ICI Americas Inc.
Wilmington, DE 19897

Dear Mr. Best:

We acknowledge the receipt on March 27, 1989 of your March 20, 1989 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 final printed labeling revised as follows to conform to labeling changes made for Merck Sharp & Dohme’s Prinivil:

1. CLINICAL PHARMACOLOGY AND OVERDOSAGE: Addition of the statement "Lisinopril can be removed by hemodialysis."

2. CONTRAINDICATIONS: Addition of a drug-class contraindication to use in patients with a history of angioedema related to previous treatment with an ACE inhibitor.

3. HOW SUPPLIED: "Dispense in a well-closed container" changed to "Dispense in a tight container;" addition of the sentence "Protect from moisture, freezing and excessive heat."

4. PRECAUTIONS, subsection Pregnancy: Third paragraph revised to read: "Fetotoxicity was demonstrated in rabbits by an increased incidence of fetal resorption at an oral dose of lisinopril at 1 mg/kg/day and by an increased incidence of incomplete ossification at the lowest dose tested (0.1 mg/kg/day). A single intravenous dose of 15 mg/kg of lisinopril administered to pregnant rabbits on gestation days 16, 21 or 26 resulted in 88% to 100% fetal death."

5. PRECAUTIONS, subsection Pregnancy: Addition of information on the outcome of the use of ACE inhibitors in humans during pregnancy.

6. PRECAUTIONS, subsection Drug Interactions: Addition of the word "close," to read ". . . initiate therapy with ZESTRIL at a dose of 5 mg daily and provide close medical supervision . . . ."

7. DOSAGE AND ADMINISTRATION, subsection Dosage Adjustment in Renal Impairment: the "greater than" sign was changed to a "greater than or equal to" sign in the sentence "For patients with creatinine clearance $\geq 10 \text{ mL/min} \leq 30 \text{ mL/min} . . . ."
In addition, the DESCRIPTION and HOW SUPPLIED sections have been revised to include a 40 mg tablet size. This tablet size was included in the original application for Zestril and was approved. At the time of approval this tablet size was not marketed and so was not included in the labeling for your product.

As noted in your April 3, 1989 telephone conversation with Ms. Kathleen Bongiovanni, the PRECAUTIONS section, subsection Hyperkalemia contains an incorrect incidence of 1.4 percent. At the time of your next printing which we expect will be by the end of April, please correct the incidence of hyperkalemia to 2.2 percent.

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.

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 Office
Telephone: (301) 443-4730

Sincerely yours,

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

21 4/11/89

Original NDA
HFD-110
HFD-110/CSO
HFD-80/DDIR
HFD-100
HFD-232 (with labeling)
HFD-730
HFD-110/KBongiovanni
sb/4/3/89; 4/6/89; 2169S
R/D: JShort/4/3/89
RVolters/O/4/89
CResnick/4/6/89
SChen/4/5/89
NMorgenstern/4/5/89

4/6/89

APPROVAL
Pediatric Use: Safety and effectiveness in children have not been established.

Euthymic Forum: (Continued)

Pediatric Use: Safety and effectiveness in children have not been established.

Gastrointestinal: Euthymic Forum: (Continued)

Pediatric Use: Safety and effectiveness in children have not been established.

Euthymic Forum: (Continued)

Pediatric Use: Safety and effectiveness in children have not been established.

Euthymic Forum: (Continued)

Pediatric Use: Safety and effectiveness in children have not been established.

Euthymic Forum: (Continued)

Pediatric Use: Safety and effectiveness in children have not been established.

Euthymic Forum: (Continued)

Pediatric Use: Safety and effectiveness in children have not been established.
APPLICATION NUMBER: NDA 19777/S4

CHEMISTRY REVIEW(S)
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<tr>
<th>1. ORGANIZATION</th>
<th>HFD-110</th>
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<td>2. NDA NUMBER</td>
<td>19-777</td>
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<td>4. AF NUMBER</td>
<td>7-612</td>
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</table>
| 3. NAME AND ADDRESS OF APPLICANT (City and State) | ICI Pharmaceuticals Group  
Wilmington, DE 19897 |
| 5. SUPPLEMENT(S) | 6. SUPPLEMENTED PROVIDES FOR:  
FPL for revised PI. |
| 8. AMENDMENTS AND OTHER (Reports, etc.) DATES | None |
| 10. PHARMACOLOGICAL CATEGORY | Antihypertensive |
| 12. RELATED IND/NDA/DMF(S) | NDA 19-558 |
| 13. DOSAGE FORM(S) | TCM |
| 14. POTENCY (iod) | 5, 10, 20 and 40 mg |
| 16. RECORDS AND REPORTS | CURRENT |  
REVIEWED | YES | NO |

18. CONCLUSIONS AND RECOMMENDATIONS
Labeling is satisfactory as far as technical aspects are concerned. APPROVAL is recommended.

REVIEWER
James H. Short
DATE COMPLETED
MAR 20 1962

DISTRIBUTION
ORIGINAL JACKET REVIEWER
DIVISION FILE
FORM FDHI 2344 (7/73) PREVIOUS EDITION MAY BE USED UNTIL SUPPLY IS EXHAUSTED

HFD-110/CSO
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19777/S4

ADMINISTRATIVE DOCUMENTS
NDA 19-777/S-004

Date of submission: March 20, 1989

Applicant: ICI Pharmaceuticals Group

Drug Name: Zestril (lisinopril) Tablets

Date of Review: April 3, 1989

Type of Submission: Special Supplement - Changes Being Effected

ICI submitted this supplement to change their Zestril labeling to conform to the approved labeling for Prinivil (Merck's product). The changes include:

**Clinical Pharmacology and Overdosage:** addition of the statement "Lisinopril can be removed by hemodialysis."

**Contraindications:** addition of a drug-class contraindication to use in patients with a history of angioedema related to previous treatment with an ACE inhibitor.

**How Supplied:** addition of the statement "Dispense in a tight container."

These changes were approved for Prinivil N19-558/S-005, on January 31, 1989.

**Precautions, subsection Pregnancy:** third paragraph revised to read: "Fetotoxicity was demonstrated in rabbits by an increased incidence of fetal resorption at an oral dose of lisinopril at 1 mg/kg/day and by an increased incidence of incomplete ossification at the lowest dose tested (0.1 mg/kg/day). A single intravenous dose of 15 mg/kg of lisinopril administered to pregnant rabbits on gestation days 16, 21 or 26 resulted in 88% to 100% fetal death."

**Precautions, subsection Drug Interactions:** addition of the word "close", to read "...initiate therapy with ZESTRIL at a dose of 5 mg daily and provide close medical supervision..."

**How Supplied:** addition of "Protect from moisture, freezing and excessive heat."

These changes were approved for Prinivil N19-558/S-001 and S-002 on October 25, 1988.
Precautions, subsection Pregnancy: addition of information on the outcome of the use of ACE inhibitors in humans during pregnancy, consistent with the labeling approved for Prinzed (N19-778). This addition was approved for Prinivil N19-558/S-004 on March 29, 1989.

Dosage and Administration, subsection Dosage Adjustment in Renal Impairment: the "greater than" sign was changed to a "greater than or equal to" sign in the sentence "For patients with creatinine clearance ≥ 10 mL/min ≤ 30 mL/min (serum creatinine ≥ 3 mg/dl)..." This change makes the Zestril labeling conform to the Prinivil labeling.

In addition, the Description and How Supplied sections have been changes to include a new 40 mg tablet size. According to Jim Short, Ph.D, the chemistry reviewer, this tablet size was included in the original application and was approved. At the time of approval, however, ICI decided not to market this tablet size.

Precautions, subsection Hyperkalemia: the incidence of hyperkalemia was changed from 2.2 to 1.4 percent. I called Mr. William Best at ICI and asked for the basis for this change. He called back on April 3, 1989 and said that he had found that it was a mistake; the number was taken from the labeling for Prinzed (lisinopril/HCTZ) and does not apply to Prinivil or Zestril. He said that ICI will be submitting labeling at the end of April to add a statement about the use of lithium and ACE inhibitors, and he said that they could correct the error at that time. I asked Dr. Lipicky and he said that that would be acceptable.

Conclusion: I have reviewed the labeling and found that the changes do conform to approved changes for the Prinivil labeling, with the exception of the incidence of hyperkalemia. I recommend that the labeling be approved with the condition that the incidence of hyperkalemia be changed back to 2.2 percent at the time of the next labeling submission, which is expected in late April.

/cc: N19-777/S-004
HFD-110
HFD-110/CSO

/S/
Kathleen Bongiovanni, CSO
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19777/S4

CORRESPONDENCE
CERTIFIED MAIL
RETURN RECEIPT REQUESTED

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

Gentlemen:

Re: ZESTRIL® (lisinopril - Stuart) Tablets
NDA 19-777
Special Supplement — Changes Being Effecte

We take this opportunity to advise you of several changes to the labeling for ZESTRIL® (lisinopril - Stuart) Tablets.

Changes have been made in response to your letters of June 21 and June 30, 1988. The letter of June 21 requested the addition of a new subheading and paragraphs entitled "HUMAN EXPERIENCE" to appear under the section "PRECAUTIONS, PREGNANCY." The letter of June 30 provided for the addition of the company name "STUART" to follow the generic name, and the trademark designation as a registered trademark symbol (ie, ®). Also, in response to the June 30 letter, the storage statement was augmented with the phrase: "Protect from moisture, freezing and excessive heat."

Additionally, ZESTRIL labeling was revised to be in agreement with the labeling changes for Prinivil effected by Merck Sharp & Dohme Research Laboratories under NDA 19-558. Specifically, these labeling changes included the following items:

1. Under the CLINICAL PHARMACOLOGY heading, the sentence: "Lisinopril can be removed by hemodialysis," was added to the subsection Pharmacokinetics and Metabolism.

2. Under the CONTRAINDICATIONS heading, the following text was added:
   
   "... and in patients with a history of angioedema related to previous treatment with an angiotensin converting enzyme inhibitor."

3. Under the PRECAUTIONS heading, subheading Hypercalcemia, the incidence of hypercalcemia was revised to 1.4%.
4. Under the **DRUG INTERACTION** heading, subheading **Hypotension** - Patients on Diuretic Therapy, the word "close" was added to the sentence so it reads: "... initiate therapy with **ZESTRIL** at a dose of 5 mg daily and provide close medical supervision ..."

5. Under the **PREGNANCY** heading, add a new subheading entitled Human Experience and its related text.

6. Under the **PREGNANCY** heading, the paragraph discussing fetotoxicity was revised to read: "Fetotoxicity was demonstrated in rabbits by an increased incidence of fetal resorption at an oral dose of lisinopril at 1 mg/kg/day and by an increased incidence of incomplete ossification at the lowest dose tested (0.1 mg/kg/day). A single intravenous dose of 15 mg/kg of lisinopril administered to pregnant rabbits on gestation-days 16, 21 or 26 resulted in 88% to 100% fetal death.

7. Under the **OVERDOSAGE** heading, the following statement was added: "Lisinopril can be removed by hemodialysis."

8. Under the **DOSEAGE AND ADMINISTRATION** heading, subheading **Dosage Adjustment in Renal Impairment**, the sentence was revised to read: "For patients with creatinine clearance $\geq$ 10 mL/min $\leq$ 30 mL/min (serum creatinine $\geq$ 3 mg/dl) ..."

Furthermore, please take notice that we have added a 40 mg tablet to the ZESTRIL product line. Accordingly, the **DESCRIPTION AND HOW SUPPLIED** section reflect this.

For your convenience, the changes in ZESTRIL labeling have been highlighted on the enclosed copies of final printed labeling (two in copy one, one in copy two and nine unbound). This revised labeling was first used in production during March 1989.

If there are further questions, please feel free to contact me.

Sincerely,

[Signature]

William A. Best
Senior Specialist, Regulatory Compliance
Drug Regulatory Affairs Department
(302) 575-2135

WAB/TKR/mjb
Attachment