CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: NDA 19777/S9

APPROVAL LETTER
ICI Pharmaceuticals Group
ICI Americas, Inc.
Attention: William J.-Kennedy, Ph.D.
Concord Pike and New Murphy Road
Wilmington, DE 19897

Dear Dr. Kennedy:

We acknowledge the receipt on September 26, 1990 of your September 20, 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 final printed labeling revised to include new adverse experiences reported since the marketing of this product. These changes include:

WARNINGS Neutropenia/Agranulocytosis: the addition of the following:

Marketing experience has revealed rare cases of neutropenia and bone marrow depression in which a casual relationship to lisinopril cannot be excluded.

ADVERSE REACTIONS:

The introductory paragraph, "Clinical adverse experiences occurring in 0.3 to 1.0 percent of patients treated with PRINIVIL monotherapy in the controlled trials and rarer, serious, possibly drug-related events reported in uncontrolled studies or marketing experience" has the following added information: "as listed below and, within each category, are in order of decreasing severity."

Body as a Whole: the addition of "malaise."

Cardiovascular: the addition of "Myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients (see WARNINGS, Hypotension);" and "vasculitis" (moved from subsection Other).

Digestive: the addition of "pancreatitis" and "dry mouth."

Nervous System/Psychiatric: the addition of "nervousness, confusion."

Urogenital: the addition of "urinary tract infection" (moved from subsection Other).
New subsections:

"Skin: Urticaria, pruritus, diaphoresis." (pruritus moved from subsection Other).

"Special Senses: the addition of "Blurred vision." (moved from subsection Other).

New paragraph: "A symptom complex has been reported which may include a positive ANA, an elevated erythrocyte sedimentation rate, arthralgia/arthritis, myalgia and fever."

Subsection deleted: Other.

Clinical Laboratory Test Findings, subsection Other (Casual Relationship Unknown): the addition of the following: "In marketing experience, rare cases of neutropenia and bone marrow depression have been reported."

In addition, minor editorial changes have been made.

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

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

Cc: Original NDA
HFD-110
HFD-110/CSO
HFD-80/DDIR
HFD-100
HFD-232 (with labeling)
HFD-730
HFD-110/KBongiovanni
sb/10/4/90;10/9/90;10/17/90/0448Q
R/D: JShort/10/10/90
RWolters/10/11/90
SChen/10/11/90
NMorgenstern/10/16/90

Approval Date: NDA 19-777 - May 19, 1988

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

RX 10/17/90
APPLICATION NUMBER: NDA 19777/S9

FINAL PRINTED LABELING
ZESTRIL
LISINOPRIL STUART

DESCRIPTION:
ZESTRIL is a diuretic, a synthetic purine derivative, it is an oral hypotensive drug containing a selective sodium channel blocker. Lisinopril is derived from the amino acid (S)-2-((3S)-1-carboxypropyl)inhetrophyphenylacetyl)l-arginine, its lactam (4S)-1-carboxypropyl)inhetrophyphenylacetyl)l-arginine and its lactam in.

Actions:
Lisinopril is a white to off-white, crystalline powder with a molecular weight of 447.6. It is a solid in water and soluble in ethanol or methanol.

ZESTRIL is supplied as 5 mg, 10 mg, 20 mg, and 40 mg tablets for oral use.

Indications:
- Hypertension: It is used in patients with essential hypertension.
- Congestive Heart Failure: It is used in patients with congestive heart failure.
- Mitral Stenosis: It is used in patients with mitral stenosis.

Chemical Name:
Lisinopril

Pharmacology:
Lisinopril is an angiotensin-converting enzyme (ACE) inhibitor.

Adverse Effects:
Common side effects include:
- Headache
- Coughing
- Diarrhea
- Constipation
- Fatigue
- Dizziness

Precautions:
- Pregnancy: Use only when clearly needed.
- Lactation: Use with caution.
- Children: Use with caution.

Applicability:
In general, the use of ZESTRIL is preferable in elderly patients with hypertension and congestive heart failure. However, the dose should be reduced in patients with impaired renal function or liver disease.

Contraindications:
ZESTRIL is contraindicated in patients with a history of angioedema, anaphylaxis, or a severe allergic reaction to angiotensin-converting enzyme inhibitors. ZESTRIL is also contraindicated in patients with a history of angioedema, anaphylaxis, or a severe allergic reaction to angiotensin-converting enzyme inhibitors.

Monitoring:
- Plasma renin activity
- Potassium levels
- Creatinine

Dosing:
- Adults: Initial dose is 5 mg daily, may be increased to 10 mg daily if necessary.
- Elderly patients: Initial dose is 2.5 mg daily, may be increased to 5 mg daily if necessary.

Interaction:
- NSAIDs: May increase the risk of renal dysfunction.
- Potassium-sparing diuretics: May increase the risk of hyperkalemia.

Laboratory Tests:
- Complete blood count
- Creatinine
- Electrolytes

References:
- ACC/AHA Guidelines for the Evaluation and Management of Essential Hypertension
- ESC Guidelines for the Management of Hypertension
- KDIGO Clinical Practice Guideline for the Management of High Blood Pressure in Adults

ZESTRIL is a trademark of Merck & Co., Inc., Kenilworth, NJ 07033 USA.

For more information, please contact your healthcare provider or visit the Merck website at www.merck.com.
ZESTRANA (metaprolol tartrate)

Pharmacology: Metaprolol is a beta-adrenergic blocking agent with little intrinsic sympathomimetic activity (ISA) and no alpha-blocking activity. The drug is a competitive antagonist at beta-adrenergic receptors, and its pharmacologic activity is mediated by a decrease in the frequency and force of cardiac contractility, a decreased rate of atrioventricular conduction, and a reduction in myocardial oxygen consumption. Metaprolol is metabolized in the liver and excreted in the urine.

Absorption: After oral administration, metaprolol is well absorbed from the gastrointestinal tract. Peak plasma concentrations are usually reached within 1 to 2 hours. The absolute bioavailability of metaprolol is approximately 50%. The drug is highly protein-bound (90% to 99%).

Distribution: Metaprolol distributes widely throughout the body, including the brain. The volume of distribution is approximately 0.25 to 0.5 liters/kg.

Metabolism: Metaprolol is extensively metabolized in the liver. The major metabolites are inactive.

Elimination: Metaprolol is primarily excreted in the urine. The elimination half-life is approximately 3 to 5 hours.

Clinical Pharmacology: ZESTRANA is used to treat hypertension, angina pectoris, and chronic stable angina. It is also effective in the management of supraventricular arrhythmias, including atrial fibrillation and atrial flutter, and in the treatment of angina pectoris in patients with coronary artery disease.

Contraindications: Metaprolol is contraindicated in patients with a history of allergic reactions to metaprolol or other beta-adrenergic blocking agents.

Liver dysfunction: Metaprolol is metabolized in the liver. Patients with hepatic dysfunction may have an increased risk of adverse effects.

Transplantation: Metaprolol is not recommended for use in patients with a history of heart transplantation.

Drug Interactions: Metaprolol may interact with other agents that affect the cardiovascular system, such as calcium channel blockers and certain antibiotics.

Dosing: The usual adult dosage for hypertension is 25 mg twice daily, administered as a single dose in the morning and evening. The dosage may be increased to 50 mg twice daily or higher, if needed. For angina pectoris, the recommended initial dosage is 25 mg twice daily, and the dosage may be increased to 50 mg twice daily or higher, if needed.

Special Populations: The safety and efficacy of ZESTRANA have not been established in children, in patients with hepatic or renal impairment, or in patients with concomitant diabetes mellitus.

Elderly Patients: In elderly patients, dose reduction may be necessary due to decreased hepatic and renal function.

Overdosage: Overdosage of metaprolol may result in hypotension, bradycardia, and conduction disturbances.

Pregnancy: Metaprolol is a category C drug and should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Lactation: Metaprolol is excreted in breast milk. The decision to discontinue breastfeeding should be made based on the importance of the drug to the mother.

Pediatric Use: The safety and efficacy of ZESTRANA in children have not been established.

Handbook of Clinical Laboratory Tests

ZESTRANA (metaprolol)

Dosage and Administration

ZESTRANA is available in 25 mg and 50 mg tablets. The recommended initial dosage for hypertension is 25 mg twice daily, administered as a single dose in the morning and evening. The dosage may be increased to 50 mg twice daily or higher, if needed. For angina pectoris, the recommended initial dosage is 25 mg twice daily, and the dosage may be increased to 50 mg twice daily or higher, if needed.

Metaprolol may be administered with or without food. The tablets can be swallowed whole or crushed and sprinkled on food. The solution should be consumed immediately and not immediately followed by any other food or drink.

Overdosage

Overdosage of metaprolol may result in hypotension, bradycardia, and conduction disturbances. The management of overdose should include supportive and symptomatic therapy. If necessary, a beta-adrenergic agonist may be given to counteract the effects of metaprolol.

Special Populations

Elderly Patients

In elderly patients, dose reduction may be necessary due to decreased hepatic and renal function. Dose adjustment should be made based on the patient's response to therapy and monitored electrocardiogram (ECG).

Children

The safety and efficacy of ZESTRANA in children have not been established. Dosing should be individualized based on the child's age and weight.

Pregnancy

Metaprolol is a category C drug and should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Lactation

Metaprolol is excreted in breast milk. The decision to discontinue breastfeeding should be made based on the importance of the drug to the mother.

Handbook of Clinical Laboratory Tests

ZESTRANA (metaprolol)

Dosage and Administration

ZESTRANA is available in 25 mg and 50 mg tablets. The recommended initial dosage for hypertension is 25 mg twice daily, administered as a single dose in the morning and evening. The dosage may be increased to 50 mg twice daily or higher, if needed. For angina pectoris, the recommended initial dosage is 25 mg twice daily, and the dosage may be increased to 50 mg twice daily or higher, if needed.

Metaprolol may be administered with or without food. The tablets can be swallowed whole or crushed and sprinkled on food. The solution should be consumed immediately and not immediately followed by any other food or drink. Storing instructions: Store at room temperature. Protect from moisture, freezing, and excessive heat. Discontinue at the nearest dosage form.
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19777/S9

CHEMISTRY REVIEW(S)
**CHEMIST’S REVIEW**

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<th>Column</th>
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<tr>
<td>2. FDA Number</td>
<td>19-777</td>
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<tr>
<td>3. Name and Address of Applicant (City &amp; State)</td>
<td>ICI Pharmaceuticals Group Wilmington, DE 19897</td>
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<td>4. AF Number</td>
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<td>5. Supplement(s) Number(s)</td>
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<td>6. Supplement(s) Date(s)</td>
<td>9/20/90</td>
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<td>7. Nonproprietary Name</td>
<td>Lisinopril</td>
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<td>8. Supplement(s) Provides For: The amendment provides responses to the Agency’s letter of 10/19/89, and to bring the labeling into agreement with that for Merck’s Prinivil.</td>
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<td>9. Amendments &amp; Other (Reports, etc) Dates</td>
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<td>N 19-558 (Prinivil Merck)</td>
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<td>13. Dosage Form(s)</td>
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<td>14. Potency(ies)</td>
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<td>15. Chemical Name and Structure</td>
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<td>16. Records &amp; Reports</td>
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<td>Current</td>
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<td>17. Comments</td>
<td>There are no changes as far as the technical aspects of the labeling are concerned.</td>
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<tr>
<td>18. Conclusions and Recommendations:</td>
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**REVIEWER**

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<thead>
<tr>
<th>Name</th>
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<tr>
<td>James R. Short</td>
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jhs/10/10/90/#19-777.809
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19777/S9

ADMINISTRATIVE DOCUMENTS
CSO Review of Labeling

NDA 19-777/S-009

Date of submission: September 20, 1990

Date of receipt: September 26, 1990

Applicant: ICI Pharmaceuticals Group, ICI Americas Inc.

Drug Name: Zestril (lisinopril) Tablets

Date of Review: September 27, 1990

Type of Submission: Special Supplement - Changes Being Effect

ICI has submitted final printed labeling revised to be in agreement with the labeling changes for Prinivil that were submitted to NDA 19-558 as supplement 008 and approved April 12, 1990. These changes include the addition of pancreatitis to the ADVERSE REACTIONS section, as we requested in a letter dated October 19, 1989, as well as other adverse experiences reported since the drug was marketed. This labeling is scheduled to be implemented into production packaging during September 1990. The changes are as follows:

WARNINGS, Neutropenia/Agranulocytosis: the addition of the following:
Marketing experience has revealed rare cases of neutropenia and bone marrow depression in which a causal relationship to lisinopril cannot be excluded.

ADVERSE REACTIONS: this section has been revised to include new adverse experiences reported since the marketing of the product. The changes include the following:

Clinical adverse experiences occurring in 0.3 to 1.0 percent of patients in the controlled trials and rarer, serious, possibly drug-related events reported in uncontrolled studies or marketing experience are listed below and, within each category, are in order of decreasing severity (underlined portion added):

Body as a Whole: addition of "malaise."
Cardiovascular: addition of "Myocardial Infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients (see WARNINGS, Hypotension);" and "vasculitis" (moved from subsection Other).
Digestive: addition of "pancreatitis" and "dry mouth."
Nervous System/Psychiatric: addition of "nervousness, confusion."
Urogenital: "urinary tract infection" (moved from subsection Other)
New subsections:
"Skin: Urticaria, pruritus, diaphoresis." (pruritus moved from subsection Other);
"Special Senses: Blurred vision." (moved from subsection Other)
Subsection deleted: Other.
Added paragraph: "A symptom complex has been reported which may include a positive ANA, an elevated erythrocyte sedimentation rate, arthralgia/arthritis, myalgia and fever."

Clinical Laboratory Tests Findings, subsection Other (Causal Relationship Unknown):
addition of the following: "In marketing experience, rare cases of neutropenia and bone marrow depression have been reported."

In addition, minor editorial changes have been made.

Conclusion: Merck submitted supporting information for the above changes to NDA 19-558/S-008; under their agreement with Merck, ICI has changed the ZESTRIL labeling to be in agreement with the PRINIVIL labeling. The changes to the labeling are allowable under 21 CFR 314.70 (c)(2)(i), supplements for changes that may be made before FDA approval. I will prepare an acknowledge and approval letter for Dr. Lipicky's signature.

/S/

Kathleen F. Bongiovanni

cc: NDA 19-777/S-009  
    HFD-110  
    HFD-111/CSO  
    HFD-111/SBenton
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)  
NDA 19-777  
Special Supplement - Changes Being Effected  

We take this opportunity to advise you of changes made to our final printed labeling for ZESTRIL® (lisinopril - Stuart). These changes have been outlined on the enclosed 3-column review document. For your convenience: the left column represents the current labeling; the middle column represents the revisions; and the right column represents comments.  

Changes have been made in response to your letter of October 19, 1989 requesting the addition of pancreatitis to the Adverse Reaction section (see page 17 of the review document).  

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 (see pages 8, 17, and 19 of the review document).  

These revisions appear in the enclosed final printed package insert Rev L 02/90 (SIC No. 63986-08) and will be implemented into production packaging during September 1990.  

Please feel free to contact me if you should have any questions.  

Sincerely,  

William A. Best  
Assistant Manager, Regulatory Compliance  
Drug Regulatory Affairs Department  
(302) 886-2135  

Enclosure  

The ICI Pharmaceuticals Group, a business unit of ICI Americas Inc., includes Stuart Pharmaceuticals and ICI Pharma.
Zestra (estradiol) is indicated for the treatment of symptoms of menopause after failure of other treatment. Zestra (estradiol) is available in 5 mg tablets for oral administration.

**Pharmacology:** Estradiol is a natural hormone that is involved in the regulation of reproductive functions in both men and women. It plays a role in the development and maintenance of secondary sexual characteristics, the regulation of the menstrual cycle, and the prevention of osteoporosis in women.

**Indications:** Zestra (estradiol) is indicated for the treatment of symptoms of menopause, including hot flashes, night sweats, and vaginal atrophy.

**Dosage and Administration:** The recommended dosage of Zestra (estradiol) for the treatment of menopausal symptoms is 1 tablet (5 mg) taken orally once daily, preferably in the evening. The dosage may be increased in 5 mg increments at monthly intervals, if needed, for a maximum of 30 mg daily.

**Contraindications:**
- Known or suspected pregnancy
- Undiagnosed abnormal genital bleeding
- Known or suspected malignancies of breast or reproductive tract
- Known or suspected thrombophlebitis or thromboembolism
- Known or suspected hyperestrogenic states
- Known or suspected liver disease

**Warnings:**
- Women with a history of breast cancer or endometrial cancer may be at increased risk of breast cancer recurrence or endometrial cancer.
- Women with a history of deep vein thrombosis or pulmonary embolism may be at increased risk of thromboembolic events.

**Precautions:**
- Women with a history of congestive heart failure or coronary artery disease may be at increased risk of cardiovascular events.

**Adverse Reactions:**
- Breast tenderness
- Vaginal bleeding
- Vaginal discharge
- Headache
- Nausea
- Vomiting
- Fatigue
- Hot flashes
- Night sweats

**Drug Interactions:**
- CYP3A4 substrates may be increased in concentration and/or effect when coadministered with Zestra (estradiol). The concomitant use of these drugs should be avoided.

**Overdose:**
- There is no specific treatment for overdose of Zestra (estradiol). In the event of overdose, supportive and symptomatic treatment should be provided.

**Anticipated and Unanticipated:**
- There are no anticipated or unanticipated adverse events associated with the use of Zestra (estradiol).

**Discontinuation:**
- Zestra (estradiol) should be discontinued if the patient experiences persistent or severe side effects or if the patient's condition does not improve.

**Dosage Forms:**
- Tablets (5 mg)

**Storage:**
- Store at room temperature, 15-30° C (59-86° F).

**Supplied:**
- Tablets (5 mg) are supplied in bottles of 100 tablets and 1000 tablets.

**Package:**
- Each bottle of Zestra (estradiol) contains 100 tablets.

**References:**

**Legal Information:**
- This information is intended for healthcare professionals and is not intended to be used for patient counseling.

**Disclaimer:**
- The information provided is for educational purposes only and is not intended to be a substitute for professional medical advice. Always consult a healthcare professional for medical advice, diagnosis, or treatment.

**Stuart Pharmaceuticals, Inc.**

**Address:**
- 1000 Washington Blvd, 5th Floor
- Nutley, NJ 07110

**Telephone:**
- 201-463-6600

**Fax:**
- 201-463-6650

**Email:**
- info@stuartpharma.com

**Website:**
- www.stuartpharma.com