CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: NDA 19777/S4

APPROVAL LETTER

NDA 19-777/S-004

APR 11 1989

ICI 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 mL/min $\leq$ 30 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 Officer
Telephone: (301) 443-4730

Sincerely yours,

R L 4/11/89

Raymond J. Lipicky, M.D.
Director
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-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
RWolters/4/4/89
CResnick/4/5/89
SChen/4/5/89
NMorgenstern/4/5/89 mam 4/6/89

APPROVAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19777/S4

FINAL PRINTED LABELING

Rev I 01/89

63966-06

PROFESSIONAL INFORMATION BROCHURE

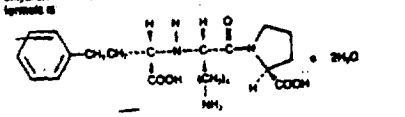
ZESTRIL®
LISINOPRIL-STUART

APR 11 1989

APPROVED

DESCRIPTION

ZESTRIL® (lisinopril), a synthetic peptide derivative, is an oral long-acting angiotensin converting enzyme inhibitor. Lisinopril is chemically described as 1-[N^2-[(*S*)-1-Carboxy-3-phenylpropyl]-L-lysyl]-L-proline dihydrate. Its empirical formula is $C_{21}H_{31}N_3O_5 \cdot 2H_2O$ and its structural formula is



Lisinopril is a white to off-white, crystalline powder, with a molecular weight of 441.53. It is soluble in water and sparingly soluble in methanol and practically insoluble in ethanol.

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

Inactive Ingredients:

5, 10 and 20 mg tablets—calcium phosphate, magnesium stearate, mannitol, red ferric oxide, starch.

40 mg tablets—calcium phosphate, magnesium stearate, mannitol, starch, yellow ferric oxide

CLINICAL PHARMACOLOGY

Mechanism of Action: Lisinopril inhibits angiotensin converting enzyme (ACE) in human subjects and animals. ACE is a peptidyl dipeptidase that catalyzes the conversion of angiotensin I to the vasoconstrictor substance, angiotensin II. Angiotensin II also stimulates aldosterone secretion by the adrenal cortex. Inhibition of ACE results in decreased plasma angiotensin II which leads to decreased vasopressor activity and to decreased aldosterone secretion. The latter decrease may result in a small increase of serum potassium. In hypertensive patients with normal renal function treated with **ZESTRIL** alone for up to 24 weeks, the mean increase in serum potassium was approximately 0.1 mEq/L; however, approximately 15% of patients had increases greater than 0.5 mEq/L and approximately 6% had a decrease greater than 0.5 mEq/L. In the same study, patients treated with **ZESTRIL** and hydrochlorothiazide for up to 24 weeks had a mean decrease in serum potassium of 0.1 mEq/L; approximately 4% of patients had increases greater than 0.5 mEq/L and approximately 12% had a decrease greater than 0.5 mEq/L. (See PRECAUTIONS.) Removal of angiotensin II negative feedback on renin secretion leads to increased plasma renin activity.

ACE is identical to kininase, an enzyme that degrades bradykinin. Whether increased levels of bradykinin, a potent vasodepressor peptide, play a role in the therapeutic effects of **ZESTRIL** remains to be elucidated.

While the mechanism through which **ZESTRIL** lowers blood pressure is believed to be primarily suppression of the renin-angiotensin-aldosterone system, **ZESTRIL** is antihypertensive even in patients with low-renin hypertension. Although **ZESTRIL** was antihypertensive in all races studied, black hypertensive patients (usually a low-renin hypertensive population) had a smaller average response to monotherapy than nonblack patients.

Concomitant administration of **ZESTRIL** and hydrochlorothiazide further reduced blood pressure in black and nonblack patients and any racial differences in blood pressure response were no longer evident.

Pharmacokinetics and Metabolism: Following oral administration of **ZESTRIL**, peak serum concentrations of lisinopril occur within about 7 hours. Declining serum concentrations exhibit a prolonged terminal phase which does not contribute to drug accumulation. This terminal phase probably represents saturable binding to ACE and is not proportional to dose. Lisinopril does not appear to be bound to other serum proteins.

Lisinopril does not undergo metabolism and is excreted unchanged entirely in the urine. Based on urinary recovery, the mean extent of absorption of lisinopril is approximately 25%, with large interindividual variability (6%-60%) at all doses tested (5-80 mg). Lisinopril absorption is not influenced by the presence of food in the gastrointestinal tract.

Upon multiple dosing, lisinopril exhibits an effective half-life of accumulation of 12 hours.

Impaired renal function decreases elimination of lisinopril, which is excreted principally through the kidneys, but this decrease becomes clinically important only when the glomerular filtration rate is below 30 mL/min. Above this glomerular filtration rate, the elimination half-life is little changed. With greater impairment, however, peak and trough blood levels increase, time to peak concentration increases and time to attain steady state is prolonged. Older patients, on average, have diminished (approximately doubled) higher blood levels and the area under the plasma concentration time curve (AUC) than younger patients. (See DOSAGE AND ADMINISTRATION.) Lisinopril can be removed by hemodialysis.

Studies in rats indicate that lisinopril crosses the blood-brain barrier very poorly. Multiple doses of lisinopril in rats do not result in accumulation in any tissues. Less of lactating rats contains radioactivity following administration of ^{14}C lisinopril. By whole body autoradiography, radioactivity was found in the placenta following administration of labeled drug to pregnant rats, but none was found in the fetuses.

Pharmacodynamics: Administration of **ZESTRIL** to patients with hypertension results in a reduction of both supine and standing blood pressure to about the same extent with no compensatory tachycardia. Symptomatic postural hypotension is usually not observed although it can occur and should be anticipated in volume and/or salt-depleted patients. (See WARNINGS.) When given together with thiazide-type diuretics, the blood pressure lowering effects of the two drugs are approximately additive.

In most patients studied, onset of antihypertensive activity was seen at one hour after oral administration of an individual dose of **ZESTRIL**, with peak reduction of blood pressure achieved by 6 hours. Although an antihypertensive effect was observed 24 hours after dosing with recommended single daily doses, the effect was more consistent and the mean effect was considerably larger in some studies with doses of 20 mg or more than with lower doses. However, at all doses studied, the mean antihypertensive effect was substantially smaller 24 hours after dosing than it was 6 hours after dosing.

In some patients achievement of optimal blood pressure reduction may require two to four weeks of therapy.

The antihypertensive effects of **ZESTRIL** are maintained during long-term therapy. Abrupt withdrawal of **ZESTRIL** has not been associated with a rapid increase in blood pressure; or a significant increase in blood pressure compared to pretreatment levels.

Two dose-response studies utilizing a once daily regimen were conducted in 438 mild to moderate hypertensive patients not on a diuretic. Blood pressure was measured 24 hours after dosing. An antihypertensive effect of **ZESTRIL** was seen with 5 mg in some patients. However, in both studies blood pressure reduction occurred sooner and was greater in patients treated with 10, 20 or 80 mg of **ZESTRIL**. In controlled clinical studies, **ZESTRIL** 20-80 mg has been compared in patients with mild to moderate hypertension to hydrochlorothiazide (12.5-50 mg and with atenolol 50-200 mg; and in patients with moderate to severe hypertension to metoprolol 100-200 mg. It was superior to hydrochlorothiazide in effects on systolic and diastolic pressure in a population that was 344 Caucasian. **ZESTRIL** was approximately equivalent to atenolol and metoprolol in effects on systolic diastolic blood pressure, and had somewhat greater effects on systolic blood pressure.

ZESTRIL had similar effectiveness and adverse effects in younger and older (> 65 years) patients. It was less effective in blacks than in Caucasians.

In hemodynamic studies in patients with essential hypertension, blood pressure reduction was accompanied by a reduction in peripheral arterial resistance with little or no change in cardiac output and in heart rate. In a study in less hypertensive patients, following administration of **ZESTRIL**, there was an increase in mean renal blood flow that was not significant. Data from several small studies are inconsistent with respect to the effect of lisinopril on glomerular filtration rate in hypertensive patients with normal renal function, but suggest that changes, if any, are not large.

In patients with renovascular hypertension **ZESTRIL** has been shown to be well tolerated and effective in controlling blood pressure. (See PRECAUTIONS.)

INDICATIONS AND USAGE:

ZESTRIL is indicated for the treatment of hypertension. It may be used alone as initial therapy or concomitantly with other classes of antihypertensive agents.

In using **ZESTRIL**, consideration should be given to the fact that another angiotensin converting enzyme inhibitor, captopril, has caused agranulocytosis, particularly in patients with renal impairment or collagen vascular disease, and that available data are insufficient to show that **ZESTRIL** does not have a similar risk. (See WARNINGS.)

CONTRAINDICATIONS:

ZESTRIL is contraindicated in patients who are hypersensitive to this product and in patients with a history of angioedema related to previous treatment with an angiotensin converting enzyme inhibitor.

WARNINGS

Angioedema: Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with angiotensin converting enzyme inhibitors, including **ZESTRIL**. In such cases, **ZESTRIL** should be promptly discontinued, and the patient carefully observed until the swelling disappears. In instances where swelling has been confined to the face and lips the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms. Angioedema associated with laryngeal edema may be fatal. Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, appropriate therapy, eg, subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL) should be promptly administered. (See ADVERSE REACTIONS.)

Hypotension: Excessive hypotension was rarely seen in uncomplicated hypertensive patients but is a possible consequence of use with **ZESTRIL** in salt/volume-depleted persons, such as those treated vigorously with diuretics or patients on dialysis. (See PRECAUTIONS, Drug Interactions and ADVERSE REACTIONS.) In patients with severe congestive heart failure, with or without associated renal insufficiency, excessive hypotension has been observed, and may be associated with oliguria and/or progressive azotemia, and rarely with acute renal failure and/or death. Because of the potential fall in blood pressure in these patients, therapy should be started under very close medical supervision. Such patients should be followed closely for the first two weeks of treatment and whenever the dose of **ZESTRIL** and/or diuretic is increased. Similar considerations apply to patients with ischemic heart or cerebrovascular disease, in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

If hypotension occurs, the patient should be placed in supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses which usually can be given without difficulty once the blood pressure has increased after volume expansion.

Neutropenia/Agranulocytosis: Another angiotensin converting enzyme inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients but more frequently in patients with renal impairment especially if they also have a collagen vascular disease. Available data from clinical trials of **ZESTRIL** are insufficient to show that **ZESTRIL** does not cause agranulocytosis at similar rates. Periodic monitoring of white blood cell counts in patients with collagen vascular disease and renal disease should be considered.

PRECAUTIONS

General

Impaired Renal Function: As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe congestive heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin converting enzyme inhibitors, including **ZESTRIL**, may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death.

In hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine may occur. Experience with another angiotensin converting enzyme inhibitor suggests that these increases are usually reversible when discontinuation of **ZESTRIL** and/or diuretic therapy is indicated. In such patients, renal function should be monitored during the first few weeks of therapy.

Some hypertensive patients with no apparent pre-existing renal vascular disease have developed increases of blood urea nitrogen and serum creatinine, usually minor and transient, especially when **ZESTRIL** has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction of **ZESTRIL** and/or discontinuation of the diuretic may be required.

Evaluation of the hypertensive patient should always include assessment of renal function. (See DOSAGE AND ADMINISTRATION.)

Hyperkalemia: In clinical trials hyperkalemia (serum potassium greater than 5.7 mEq/L) occurred in approximately 1.4% of hypertensive patients and 4.0% of patients with congestive heart failure. In most cases these were isolated values which resolved despite continued therapy. Hyperkalemia was a cause of discontinuation of therapy in approximately 0.1% of hypertensive patients. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with **ZESTRIL**. (See Drug Interactions.)

Surgery/Anesthesia: In patients undergoing major surgery or during anesthesia with agents that produce hypotension, **ZESTRIL** may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Information for Patients

Angioedema: Angioedema, including laryngeal edema, may occur especially following the first dose of **ZESTRIL**. Patients should be advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to take no more drug until they have consulted with the prescribing physician.

Symptomatic Hypotension: Patients should be cautioned to report lightheadedness especially during the first few days of therapy. If actual syncope occurs, the patient should be told to discontinue the drug until they have consulted with the prescribing physician.

All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure; patients should be advised to consult with their physician.

Hyperkalemia: Patients should be told not to use salt substitutes containing potassium without consulting their physician.

Neutropenia: Patients should be told to report promptly any indication of infection (eg, sore throat, fever) which may be a sign of neutropenia.

Note: As with many other drugs, certain advice to patients being treated with **ZESTRIL** is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

DRUG INTERACTIONS

Hypotension—Patients on Diuretic Therapy: Patients on diuretics and especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with **ZESTRIL**. The possibility of hypotensive effects with **ZESTRIL** can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with **ZESTRIL**. If it is necessary to continue the diuretic, initiate therapy with **ZESTRIL** at a dose of 5 mg daily, and provide close medical supervision after the initial dose for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS, and DOSAGE AND ADMINISTRATION.) When a diuretic is added to the therapy of a patient receiving **ZESTRIL**, an additional antihypertensive effect is usually observed. Studies with ACE inhibitors in combination with diuretics indicate that the dose of the ACE inhibitor can be reduced when it is given with a diuretic. (See DOSAGE AND ADMINISTRATION.)

Indomethacin: In a study in 36 patients with mild to moderate hypertension where the antihypertensive effects of **ZESTRIL** alone were compared to **ZESTRIL** given concomitantly with indomethacin, the use of indomethacin was associated with a reduced effect, although the difference between the two regimens was not significant.

CONTINUED ON REVERSE SIDE

ZESTRIL® (lisinopril/Merck) (cont'd)

Other Agents: ZESTRIL has been used concomitantly with studies and/or digoxin without evidence of clinically significant adverse interactions.

No clinically important pharmacokinetic interactions occurred when ZESTRIL was used concomitantly with propranolol or hydrochlorothiazide. The presence of food in the stomach does not affect the bioavailability of ZESTRIL.

Agents Increasing Serum Potassium: ZESTRIL attenuates potassium loss caused by thiazide-type diuretics. Use of ZESTRIL with potassium-sparing diuretics (eg, spironolactone, triamterene or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Therefore, if concomitant use of these agents is indicated because of demonstrated hypokalemia, they should be used with caution and with frequent monitoring of serum potassium.

Carcinogenesis, Mutagenesis, Impairment of Fertility: There was no evidence of a tumorigenic effect when lisinopril was administered for 105 weeks to male and female rats at doses up to 90 mg/kg/day (about 56 times* the maximum recommended daily human dose) or when lisinopril was administered for 92 weeks to male and female mice at doses up to 135 mg/kg/day (about 84 times* the maximum recommended daily human dose).

*Based on patient weight of 60 kg.

Lisinopril was not mutagenic in the Ames microbial mutagen test with or without metabolic activation. It was also negative in a forward mutation assay using Chinese hamster lung cells. Lisinopril did not produce single strand DNA breaks in an in vitro alkaline elution rat hepatocyte assay. In addition, lisinopril did not produce increases in chromosomal aberrations in an in vitro test in Chinese hamster ovary cells or in an in vivo study in mouse bone marrow.

There were no adverse effects on reproductive performance in male and female rats treated with up to 300 mg/kg/day of lisinopril.

Pregnancy

Pregnancy Category C: Lisinopril was not teratogenic in mice treated on days 6-15 of gestation with up to 1,000 mg/kg/day (625 times the maximum recommended human dose). There was an increase in fetal resorptions at doses down to 100 mg/kg; at doses of 1,000 mg/kg this was prevented by saline supplementation. There was no teratogenicity or tumorigenicity in rats treated with up to 300 mg/kg/day (188 times the maximum recommended dose) of lisinopril on days 6-17 of gestation. In rats receiving lisinopril from day 15 of gestation through day 21 postpartum, there was an increased incidence in pup deaths on days 3-7 postpartum and a lower average body weight of pups on day 21 postpartum. The increase in pup deaths and decrease in pup weight did not occur with maternal saline supplementation.

Lisinopril, at doses up to 1 mg/kg/day, was not teratogenic when given throughout the organogenic period in saline supplemented rabbits. Saline supplementation (physiologic saline in place of tap water) was used to eliminate hypotensive effects and enable evaluation of the teratogenic potential at the highest possible dosage level. The rabbit has been shown to be extremely sensitive to angiotensin converting enzyme inhibitors (captopril and enalapril) with maternal and fetotoxic effects apparent at or below the recommended therapeutic dosage levels in man.

Fetotoxicity was demonstrated in rabbits by an increased incidence of fetal resorptions 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 89% to 100% fetal death.

By whole body autoradiography, radioactivity was found in the placenta following administration of labeled lisinopril to pregnant rats, but none was found in the fetuses.

Human Experience: There are no adequate and well-controlled studies of lisinopril in pregnant women. However, data are available that show drugs of this class cross the human placenta. Because the risk of fetal toxicity with the use of ACE inhibitors has not been clearly defined (see below), lisinopril should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Postmarketing experience with all ACE inhibitors thus far suggests the following with regard to pregnancy outcome. Inadvertent exposure limited to the first trimester of pregnancy has not been reported to affect fetal outcome adversely. Fetal exposure during the second and third trimesters of pregnancy has been associated with fetal and neonatal morbidity and mortality.

When ACE inhibitors are used during the later stages of pregnancy, there have been reports of hypotension and decreased renal perfusion in the newborn. Oligohydramnios in the mother has also been reported, presumably representing decreased renal function in the fetus. Infants exposed in utero to ACE inhibitors should be closely observed for hypotension, oliguria and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion with the administration of fluids and pressors as appropriate. Prematurity associated with prematurity such as patent ductus arteriosus have occurred in association with maternal use of ACE inhibitors, but it is not clear whether they are related to ACE inhibition, maternal hypertension or the underlying prematurity.

Another ACE inhibitor, enalapril, has been diffused from the maternal circulation by peritoneal dialysis and theoretically may be removed by exchange transfusion, although there is no experience with the latter procedure. There is no experience with either of these procedures for removing lisinopril or other ACE inhibitors from the neonatal circulation.

Nursing Mothers: Milk of lactating rats contains radioactivity following administration of ^{14}C lisinopril. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ZESTRIL is given to a nursing mother.

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

ADVERSE REACTIONS

ZESTRIL has been found to be generally well tolerated in controlled clinical trials involving 3660 patients and subjects.

The most frequent clinical adverse experiences in controlled trials with ZESTRIL were dizziness (6.3%), headache (5.3%), fatigue (3.3%), diarrhea (3.2%), upper respiratory symptoms (3.0%), and cough (2.9%), all of which were more frequent than in placebo-treated patients. For the most part, adverse experiences were mild and transient in nature. Discontinuation of therapy was required in 6.0% of patients. In clinical trials, the overall frequency of adverse experiences could not be related to total daily dosage within the recommended therapeutic dosage range.

For adverse experiences which occurred in more than 1% of patients and subjects treated with ZESTRIL or ZESTRIL plus hydrochlorothiazide in controlled clinical trials, comparative incidence data are listed in the table below.

Percent of Patients in Controlled Studies

	ZESTRIL (n=3660†) Incidence (discontinuation)	ZESTRIL/ Hydrochlorothiazide (n=644) Incidence (discontinuation)	Placebo (n=397) Incidence
Dizziness	6.3 (0.8)	9.0 (0.9)	1.8
Headache	5.3 (0.2)	4.3 (0.6)	1.8
Fatigue	3.3 (0.2)	3.9 (0.5)	1.8
Diarrhea	3.2 (0.3)	2.8 (0.3)	2.4
Upper Respiratory Symptoms	3.0 (0.0)	4.5 (0.0)	0.0
Cough	2.9 (0.4)	4.3 (0.0)	1.0
Nausea	2.3 (0.3)	2.5 (0.2)	2.4
Hypotension	1.8 (0.0)	1.8 (0.5)	0.5
Rash	1.3 (0.4)	1.8 (0.2)	0.5
Orthostatic Effects	1.4 (0.0)	3.4 (0.2)	1.0
Asthenia	1.3 (0.4)	2.0 (0.0)	1.0
Chest Pain	1.3 (0.1)	1.2 (0.2)	1.4
Vomiting	1.3 (0.2)	1.4 (0.8)	0.5
Dyspnea	1.1 (0.0)	0.5 (0.2)	1.4
Dyspepsia	1.0 (0.0)	1.9 (0.0)	0.0
Paresthesia	0.8 (0.0)	2.0 (0.2)	0.0
Impotence	0.7 (0.2)	1.0 (0.3)	0.0
Muscle Cramps	0.6 (0.0)	2.3 (0.0)	0.5
Back Pain	0.5 (0.0)	1.1 (0.0)	1.4
Nasal Congestion	0.3 (0.0)	1.2 (0.0)	0.0
Decreased Libido	0.2 (0.1)	1.2 (0.0)	0.0
Vertigo	0.1 (0.0)	1.1 (0.2)	0.5

†Includes 429 patients treated for congestive heart failure who were receiving concomitant digitalis and/or diuretic therapy.

Clinical adverse experiences occurring in 0.3% to 1.0% of patients in the controlled trials and rarer, serious, possibly drug related events reported in uncontrolled studies or marketing experience included:

BODY AS A WHOLE: Chest discomfort, fever, flushing.

CARDIOVASCULAR: Angina pectoris, orthostatic hypotension, rhythm disturbances, tachycardia, peripheral edema, palpitation.

DIGESTIVE: Abdominal pain, anorexia, constipation, flatulence.

METABOLISM: Gout

MUSCULOSKELETAL: Joint pain, shoulder pain.

NERVOUS SYSTEM/PSYCHIATRIC: Depression, somnolence, insomnia, stroke.

RESPIRATORY SYSTEM: Bronchitis, sinusitis, pharyngeal pain.

UROGENITAL: Oliguria, progressive azotemia, acute renal failure.

OTHER: Blurred vision, pruritus, urinary tract infection, vasculitis of the legs.

ANGIOEDEMA: Angioedema has been reported in patients receiving ZESTRIL (0.1%). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis and/or larynx occurs, treatment with ZESTRIL should be discontinued and appropriate therapy instituted immediately. (See WARNINGS.)

HYPOTENSION: In hypertensive patients, hypotension occurred in 1.2% and syncope occurred in 0.1% of patients. Hypotension or syncope was a cause of discontinuation of therapy in 0.3% of hypertensive patients. (See WARNINGS.)

In patients with congestive heart failure, hypotension occurred in 5.8% and syncope occurred in 1.0% of patients. These adverse experiences were causes for discontinuation of therapy in 1.3% of these patients.

Clinical Laboratory Test Findings

Serum Electrolytes: Hyperkalemia (See PRECAUTIONS.)

Creatinine, Blood Urea Nitrogen: Minor increases in blood urea nitrogen and serum creatinine, reversible upon discontinuation of therapy, were observed in about 2.0% of patients with essential hypertension treated with ZESTRIL alone. Increases were more common in patients receiving concomitant diuretics and in patients with renal artery stenosis. (See PRECAUTIONS.) Reversible minor increases in blood urea nitrogen and serum creatinine were observed in approximately 0.1% of patients with congestive heart failure on concomitant diuretic therapy. Frequently, these abnormalities resolved when the dosage of the diuretic was decreased.

Hemoglobin and Hematocrit: Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.4 g% and 1.3 vol%, respectively) occurred frequently in patients treated with ZESTRIL but were rarely of clinical importance in patients without some other cause of anemia. In clinical trials, less than 0.1% of patients discontinued therapy due to anemia.

Other (Causal Relationship Unknown): Rarely, elevations of liver enzymes and/or serum bilirubin have occurred.

Overall, 2.8% of patients discontinued therapy due to laboratory adverse experiences, principally elevations in blood urea nitrogen (0.8%), serum creatinine (0.5%) and serum potassium (0.4%).

OVERDOSAGE

The oral LD_{50} of lisinopril is greater than 20 g/kg in mice and rats. The most likely manifestation of overdosage would be hypotension, for which the usual treatment would be intravenous infusion of normal saline solution.

Lisinopril can be removed by hemodialysis.

DOSAGE AND ADMINISTRATION

Initial therapy in patients with uncomplicated essential hypertension not on diuretic therapy: the recommended initial dose is 10 mg once a day. Dosage should be adjusted according to blood pressure response. The usual dosage range is 20-40 mg per day administered in a single daily dose. The antihypertensive effect may diminish toward the end of the dosing interval regardless of the administered dose, but most commonly with a dose of 10 mg daily. This can be evaluated by measuring blood pressure just prior to dosing to determine whether antihypertensive control is being maintained for 24 hours. If it is not, an increase in dose should be considered. Doses up to 80 mg have been used but do not appear to give greater effect. If blood pressure is not controlled with ZESTRIL alone, a low dose of a diuretic may be added. Hydrochlorothiazide, 12.5 mg has been shown to provide an additive effect. After the addition of a diuretic, it may be possible to reduce the dose of ZESTRIL.

Diuretic-Treated Patients: In hypertensive patients who are currently being treated with a diuretic, symptomatic hypotension may occur occasionally following the initial dose of ZESTRIL. The diuretic should be discontinued, if possible, for two to three days before beginning therapy with ZESTRIL to reduce the likelihood of hypotension. (See WARNINGS.) The dosage of ZESTRIL should be adjusted according to blood pressure response. If the patient's blood pressure is not controlled with ZESTRIL alone, diuretic therapy may be resumed as described above.

If the diuretic cannot be discontinued, an initial dose of 5 mg should be used under medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and PRECAUTIONS, Drug Interactions.)

Concomitant administration of ZESTRIL with potassium supplements, potassium salt substitutes, or potassium-sparing diuretics may lead to increases of serum potassium. (See PRECAUTIONS.)

Use in Elderly: In general, blood pressure response and adverse experiences were similar in younger and older patients given similar doses of ZESTRIL. Pharmacokinetic studies, however, indicate that maximum blood levels and area under the plasma concentration time curve (AUC) are doubled in older patients so that dosage adjustments should be made with particular caution.

Dosage Adjustment in Renal Impairment: The usual dose of ZESTRIL (10 mg) is recommended for patients with creatinine clearance > 30 mL/min (serum creatinine of up to approximately 3 mg/dL). For patients with creatinine clearance 10 mL/min ≤ 30 mL/min (serum creatinine ≥ 3 mg/dL), the first dose is 5 mg once daily. For patients with creatinine clearance <10 mL/min (usually on hemodialysis) the recommended initial dose is 2.5 mg. The dosage may be titrated upward until blood pressure is controlled or to a maximum of 40 mg daily.

Renal Status	Creatinine Clearance mL/min	Initial Dose mg/day
Normal Renal Function to Mild Impairment	>30	10
Moderate to Severe Impairment	≥ 10 ≤ 30	5
Dialysis Patients	<10	2.5††

††Dosage or dosing interval should be adjusted depending on the blood pressure response.

HOW SUPPLIED

5 mg Tablets (NDC 0038-0130) pink, round, biconvex, uncoated, scored tablets, embossed "ZESTRIL 5" debossed on one side, and "130" debossed and scored on the other side are supplied in bottles of 100 tablets and unit dose packages of 100 tablets.

10 mg Tablets (NDC 0038-0131) pink, round, biconvex, uncoated tablets embossed "ZESTRIL 10" debossed on one side, and "131" debossed on the other side are supplied in bottles of 100 tablets and unit dose packages of 100 tablets.

20 mg Tablets (NDC 0038-0132) red, round, biconvex, uncoated tablets identified "ZESTRIL 20" debossed on one side, and "132" debossed on the other side are supplied in bottles of 100 tablets and unit dose packages of 100 tablets.

40 mg Tablets (NDC 0038-0134) yellow, round, biconvex, uncoated tablets identified "ZESTRIL 40" debossed on one side, and "134" debossed on the other side are supplied in bottles of 100 tablets and unit dose packages of 100 tablets.

Store at room temperature. Protect from moisture. Freezing and excessive heat. Dispense in a tight container.

STUART PHARMACEUTICALS | Div of ICI Americas Inc
WILMINGTON, DELAWARE 19897

Rev I 01/89

63038-06

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19777/S4

CHEMISTRY REVIEW(S)

MAR 30 1989

CHEMIST'S REVIEW
(If necessary, continue any item on 8½" x 10½" paper. Key continuation to item by number.)

1. ORGANIZATION	2. NDA NUMBER
HFD-110	19-777

3. NAME AND ADDRESS OF APPLICANT (City and State)
ICI Pharmaceuticals Group
Wilmington, DE 19897

4. AF NUMBER
7-612

5. SUPPLEMENT (S)

NUMBER(S)	DATE(S)
S004	3/20/89

6. NAME OF DRUG
Zestril Tablets

7. NONPROPRIETARY NAME
Lisinopril

8. SUPPLEMENT(S) PROVIDES FOR:
FPL for revised PI.

9. AMENDMENTS AND OTHER (Reports, etc.) DATES
None

10. PHARMACOLOGICAL CATEGORY
Antihypertensive

11. HOW DISPENSED
☒ Rx ☐ OTC

12. RELATED IND/NDA/DMF(S)
NDA 19-558

13. DOSAGE FORM (S)
TCM

14. POTENCY (Iso)
5, 10, 20 and 40 mg

15. CHEMICAL NAME AND STRUCTURE

16. RECORDS AND REPORTS
CURRENT ☐ YES ☐ NO
REVIEWED ☐ YES ☐ NO

17. COMMENTS

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

19. REVIEWER
NAME: James H. Short
/S/
DATE COMPLETED: MAR 29 1989

DISTRIBUTION ■ ORIGINAL JACKET ☐ REVIEWER ☐ DIVISION FILE

FORM FDA 2266 (7/75) 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

CSO Review of Labeling APR 11 1989

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 Prinzide (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 $\geq$10 mL/min $\leq$ 30 mL/min (serum creatinine $\geq$ 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 Prinzide (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.

/S/

Kathleen Bongiovanni, CSO

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19777/S4

CORRESPONDENCE

COPY 1

ICI Pharmaceuticals Group

ICI Pharma
Stuart Pharmaceuticals

NDA NO. 19-777 REF. NO. S-003
NDA SUPPL FOR S.E. with
FPL

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

MAR 2 0 1989

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 Effected

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%.

ORIGINAL

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 **DOSAGE 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,

William A Best

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

WAB/TKR/mjb
Attachment