CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: NDA 19777/S9

APPROVAL LETTER

OCT 17 1990

NDA 19-777/S-009

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

Sincerely yours,

10-17-90 RX 10/17/90

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/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

APPROVAL ____

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19777/S9

FINAL PRINTED LABELING

PROFESSIONAL INFORMATION BRIEF

ZESTRIL®

LISINOPRIL-STUART

DESCRIPTION

ZESTRIL® (lisinopril), a synthetic peptide derivative, is an oral long-acting angiotensin converting enzyme inhibitor. Lisinopril is chemically described as (S)-1-[N²-(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 dose dimension in blood pressure response were no longer evident.

Pharmacokinetics and Absorption: 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 lisinopril levels increase, time to peak concentration increases and time to attain steady state is prolonged. Older patients, on average, have 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 poorly. Multiple doses of lisinopril in rats do not result in accumulation in any tissues. Milk of lactating rats contains radioactivity following administration of ^{14}C-labeled. 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 supine and standing blood pressure to about the same extent as that seen with the use of most other antihypertensive agents. 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 dose 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, in 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 34% Caucasian. ZESTRIL was approximately equivalent to atenolol and metoprolol in effects on 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 renal 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 primary 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. Marketing experience has revealed rare cases of neutropenia and bone marrow depression in which a causal relationship to lisinopril cannot be excluded. 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 expected 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 upon discontinuation of ZESTRIL and/or diuretic therapy. 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 in 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 2.2% 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 so 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 unintended 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.

Other Agents: ZESTRIL has been used concomitantly with nitrates 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 alter 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.

Lithium: Lithium toxicity has been reported in patients receiving lithium with drugs which cause elimination of sodium, including ACE inhibitors. Lithium toxicity was usually reversible upon discontinuation of both drugs. It is recommended that serum lithium levels be monitored frequently if ZESTRIL is administered concomitantly with lithium.

CONTINUED ON REVERSE SIDE

ZESTRIL® (lisinopril/Stuart)

Carcinogenesis, Mutagenesis, Impairment of Fertility: There was no evidence of a tumorigenic effect when lisinopril was administered for 105 weeks to mice and female rats at doses up to 80 mg/kg/day (about 50 times* the maximum recommended daily human dose) or when lisinopril was administered for 52 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 50 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 embryotoxicity 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 2-7 postpartum and a lower average body weight (at birth and 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 table in place of tap water) was used to eliminate maternal/renal 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 fetal/renal 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 of 1 mg/kg/day and by an increased incidence of intrauterine sacrifices 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 14, 21 or 28 resulted in 80% 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.

Nursing Mothers: 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. Involvement exclusive 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 fetal 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. Problems 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 removed from the neonatal 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 2003 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 (3.6%), and cough (2.6%), 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 5.6% 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=2003†) Incidence (discontinuation)	ZESTRIL/ Hydrochlorothiazide (n=644) Incidence (discontinuation)	Placebo (n=397) Incidence
Dizziness	6.3 (0.6)	9.9 (0.9)	1.9
Headache	5.3 (0.2)	4.3 (0.5)	1.8
Fatigue	3.3 (0.2)	3.9 (0.5)	1.8
Diarrhea	3.2 (0.2)	2.6 (0.3)	2.4
Upper Respiratory Symptoms	3.6 (0.0)	4.5 (0.6)	0.8
Cough	2.6 (0.4)	4.5 (0.6)	1.8
Nausea	2.3 (0.2)	2.8 (0.2)	2.4
Hypotension	1.6 (0.5)	1.5 (0.5)	0.5
Rash	1.5 (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 (0.2)	1.0
Chest Pain	1.3 (0.1)	1.2 (0.2)	1.4
Vomiting	1.3 (0.2)	1.4 (0.6)	0.5
Dyspnea	1.1 (0.0)	0.6 (0.2)	1.4
Dyspepsia	1.0 (0.0)	1.9 (0.0)	0.8
Paresthesia	0.6 (0.0)	2.0 (0.2)	0.8
Impotence	0.7 (0.2)	1.0 (0.3)	0.0
Muscle Cramps	0.6 (0.0)	2.5 (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)	0.0

†Includes 459 patients treated for congestive heart failure who were receiving concomitant digitalis and/or diuretic therapy.

Clinical adverse experiences occurring in 0.3% to 1.2% 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.

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

CARDIOVASCULAR: Myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients (see WARNINGS), hypotension, angina pectoris, orthostatic hypotension, rhythm disturbances, tachycardia, peripheral edema, vasculitis, palpitation.

DIGESTIVE: Pancreatitis, abdominal pain, anorexia, constipation, flatulence, dry mouth.

METABOLISM: Gout

MUSCULOSKELETAL: Joint pain, shoulder pain.

NERVOUS SYSTEM/PSYCHIATRIC: Depression, somnolence, insomnia, ataxia, nervousness, confusion

RESPIRATORY SYSTEM: Bronchitis, sinusitis, pharyngeal pain

SKIN: Urticaria, pruritus, diaphoresis.

SPECIAL SENSES: Blurred vision

UROGENITAL: Oliguria, progressive azotemia, acute renal failure, urinary tract infection

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

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 0.5% of hypertensive patients. (See WARNINGS.)

In patients with congestive heart failure, hypotension occurred in 5.8% and syncope occurred in 1.9% 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 2.8% 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 9.1% 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.

Liver (Causal Relationship Unknown): Rarely, elevations of liver enzymes and/or serum bilirubin have occurred. In marketing experience, rare cases of hepatocellular and bone marrow depression have been reported.

Overall, 2.0% of patients discontinued therapy due to laboratory adverse experiences, principally elevations in blood urea nitrogen (0.8%), serum creatinine (0.3%) 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 satisfactory 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.

Patients Titrated 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 in 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 0030-0130) pink, round, biconvex, uncoated, scored tablets, identified "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 0030-0131) pink, round, biconvex, uncoated tablets identified "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 0030-0132) 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 0030-0134) 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
A business unit of ICI Americas Inc.
Wilmington, Delaware 19897 USA

43000-00 Rev L 02/00

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19777/S9

CHEMISTRY REVIEW(S)

Vol-11.1

OCT 11 1990

CHEMIST'S REVIEW	1. Organization HFD-110	2. NDA Number 19-777
3. Name and Address of Applicant (City & State) ICI Pharmaceuticals Group Wilmington, DE 19897		4. AP Number 7-612 5. Supplement(s) Number(s): S009 Date(s): 9/20/90
6. Name of Drug Zestril	7. Nonproprietary Name Lisinopril	9. Amendments & Other (Reports, etc) Dates
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.		
10. Pharmacological Category Antihypertensive	11. How Dispensed /X/ RX / / OTC	12. Related IND/NDA/DMF N 19-558 (Prinivil Merck)
13. Dosage Form(s) TCM	14. Potency(ies) 5, 10, 20 and 40 mg	
15. Chemical Name and Structure		16. Records & Reports Current / / Yes / / No Reviewed / / Yes / / No

17. Comments

There are no changes as far as the technical aspects of the labeling are concerned.

18. Conclusions and Recommendations:

APPROVAL is recommended as far as the technical aspects of the labeling are concerned.

19. REVIEWER

Name	Signature	Date Completed
James H. Short	/S/	10/10/90

/ / Original Jacket / /Reviewer / / Div. File / / CSO

jhs/10/10/90/N19-777.S09

10/11/90

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 Effected

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 Test 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. Bonglovanni

cc: NDA 19-777/S-009
HFD-110
HFD-111/CSO
HFD-111/SBenton

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19777/S9

CORRESPONDENCE

Pharmaceuticals Group

Stuart Pharmaceuticals/ICI Pharma

ICI Pharmaceuticals Group
Wilmington
Delaware 19897 USA

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

SEP 20 1990

NDA NO. 19-777 REF. NO. 6-009
NDA SUPPL FOR SLR 09

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 /SLR

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

WAB/SLR/mjb
Enclosure

ORIGINAL

ZESTRIL® (lisinopril)

...ing 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.

Pregnancy: Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to ACE inhibitors, and they should also be told that these consequences do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

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 undesired 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.

Other Agents: ZESTRIL has been used concomitantly with nitrates 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.

Lithium: Lithium toxicity has been reported in patients receiving lithium with drugs which cause elimination of sodium, including ACE inhibitors. Lithium toxicity was usually reversible upon discontinuation of both drugs. It is recommended that serum lithium levels be monitored frequently if ZESTRIL is administered concomitantly with lithium.

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 50 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 Categories C (first trimester) and D (second and third trimesters). See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

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 2895 patients and subjects.

The most frequent clinical adverse experiences in controlled trials with ZESTRIL were dizziness (5.7%), headache (5.3%), fatigue (3.3%), diarrhea (3.2%), upper respiratory symptoms (3.0%), and cough (2.5%), 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 6.9% 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=3563†) Incidence (discontinuation)		Hydrochlorothiazide (n=644) Incidence (discontinuation)		Placebo (n=597) Incidence
Dizziness	6.3	(0.6)	9.9	(0.9)	1.9
Headache	5.3	(0.2)	4.3	(0.5)	1.3
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)	0.8
Cough	2.5	(0.4)	4.5	(0.8)	1.0
Rhinitis	2.3	(0.3)	2.5	(0.2)	2.4
Hypotension	1.8	(0.8)	1.8	(0.8)	0.5
Rash	1.5	(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	(0.2)	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
Dyspepsia	1.1	(0.0)	0.5	(0.2)	1.4
Syncope	1.0	(0.6)	1.9	(0.8)	0.8
Paresthesia	0.8	(0.6)	2.0	(0.2)	0.8
Impotence	0.7	(0.2)	1.6	(0.3)	0.8
Muscle Cramps	0.6	(0.0)	2.0	(0.6)	0.5
Back Pain	0.5	(0.0)	1.1	(0.0)	1.4
Nasal Congestion	0.3	(0.0)	1.2	(0.0)	0.8
Decreased Libido	0.2	(0.1)	1.2	(0.0)	0.0
Vertigo	0.1	(0.0)	1.1	(0.2)	0.8

†Includes 439 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 are listed below and, within each category, are in order of decreasing severity.

BODY AS A WHOLE: Anaphylactoid Reactions (see PRECAUTIONS - Hemodialysis Patients), chest discomfort, fever, flushing, malaise.

CARDIOVASCULAR: Myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients (see WARNINGS, Hypotension); angina pectoris, orthostatic hypotension, rhythm disturbances, tachycardia, peripheral edema, vasculitis, palpitation.

DIGESTIVE: Pancreatitis, hepatitis (hepatocellular or cholestatic jaundice), abdominal pain, anorexia, constipation, flatulence, dry mouth.

METABOLISM: Gout

MUSCULOSKELETAL: Joint pain, shoulder pain.

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

RESPIRATORY SYSTEM: Bronchitis, sinusitis, pharyngeal pain.

SKIN: Urticaria, pruritus, diaphoresis, photosensitivity.

SPECIAL SENSES: Blurred vision.

UROGENITAL: Oliguria, progressive azotemia, acute renal failure, urinary tract infection.

Miscellaneous: A symptom complex has been reported which may include a positive ANA, an elevated erythrocyte sedimentation rate, arthralgia/arthritis, myalgia, fever, vasculitis, eosinophilia and leukocytosis. Rash, photosensitivity or other dermatological manifestations may occur alone or in combination with these symptoms.

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 0.5% of hypertensive patients. (See WARNINGS.)

In patients with congestive heart failure, hypotension occurred in 5.6% and syncope occurred in 1.6% of patients. These adverse experiences were causes for discontinuation of therapy in 1.3% of these patients.

Fetal/Neonatal Morbidity and Mortality: See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

Cough: See PRECAUTIONS - Cough

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 0.11% 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. In marketing experience, rare cases of neutropenia and bone marrow depression have been reported.

Overall, 2.0% of patients discontinued therapy due to laboratory adverse experiences, principally elevations in blood urea nitrogen (0.6%), serum creatinine (0.5%) and serum potassium (0.7%).

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 20-60 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 satisfactory 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**

*See PRECAUTIONS, Hemodialysis Patients.

**Dosage interval should be adjusted depending on the blood pressure response.

HOW SUPPLIED

5 mg Tablets (NDC 0000-0130) pink, capsule-shaped, biconvex, beveled, uncoated tablets, identified "ZESTRIL" on one side and "130" on the other side are supplied in bottles of 100 tablets and 1000 tablets, and unit dose packages of 100 tablets.

10 mg Tablets (NDC 0000-0131) pink, round, biconvex, uncoated tablets identified "ZESTRIL 10" debossed on one side, and "131" debossed on the other side are supplied in bottles of 100 tablets and 1000 tablets, and unit dose packages of 100 tablets.

20 mg Tablets (NDC 0000-0132) 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 1000 tablets, and unit dose packages of 100 tablets.

40 mg Tablets (NDC 0000-0134) 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.

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STUART PHARMACEUTICALS
A business unit of ICI Americas Inc.
Wilmington, Delaware 19897 USA

0000-13 Rev I 00/00