TABLETS

PRINIVIL®

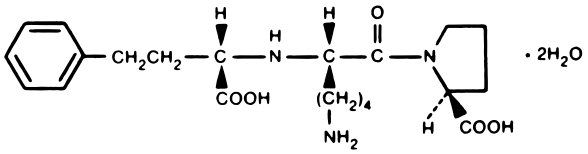
(LISINOPRIL)

USE IN PREGNANCY

When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, PRINIVIL should be discontinued as soon as possible. See WARNINGS, *Fetal/Neonatal Morbidity and Mortality*.

DESCRIPTION

PRINIVIL* (Lisinopril), a synthetic peptide derivative, is an oral long-acting angiotensin converting enzyme inhibitor. Lisinopril is chemically described as (*S*)-1-[*N*2-(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 441.52. It is soluble in water and sparingly soluble in methanol and practically insoluble in ethanol.

PRINIVIL is supplied as 2.5 mg, 5 mg, 10 mg, 20 mg and 40 mg tablets for oral administration. In addition to the active ingredient lisinopril, each tablet contains the following inactive ingredients: calcium phosphate, mannitol, magnesium stearate, and starch. The 10 mg, 20 mg and 40 mg tablets also contain iron 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. The beneficial effects of lisinopril in hypertension and heart failure appear to result primarily from suppression of the renin-angiotensin-aldosterone system. 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 PRINIVIL alone for up to 24 weeks, the mean increase in serum potassium was approximately 0.1 mEq/L; however, approximately 15 percent of patients had increases greater than 0.5 mEq/L and approximately six percent had a decrease greater than 0.5 mEq/L. In the same study, patients treated with PRINIVIL and hydrochlorothiazide for up to 24 weeks had a mean decrease in serum potassium of 0.1 mEq/L; approximately 4 percent of patients had increases greater than 0.5 mEq/L and approximately 12 percent 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 PRINIVIL remains to be elucidated.

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

Concomitant administration of PRINIVIL and hydrochlorothiazide further reduced blood pressure in Black and non-Black patients and any racial difference in blood pressure response was no longer evident.

Pharmacokinetics and Metabolism

Adult Patients: Following oral administration of PRINIVIL, peak serum concentrations of lisinopril occur within about 7 hours, although there was a trend to a small delay in time taken to reach peak serum concentrations in acute myocardial infarction patients. 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 percent, with large inter-subject variability (6-60 percent) at all doses tested (5-80 mg). Lisinopril absorption is not influenced by the presence of food in the gastrointestinal tract. The absolute bioavailability of lisinopril is reduced to about 16 percent in patients with stable NYHA Class II-IV congestive heart failure, and the volume of distribution appears to be slightly smaller than that in normal subjects.

The oral bioavailability of lisinopril in patients with acute myocardial infarction is similar to that in healthy volunteers.

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 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 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.

Pediatric Patients: The pharmacokinetics of lisinopril were studied in 29 pediatric hypertensive patients between 6 years and 16 years with glomerular filtration rate >30 mL/min/1.73 m^2. After doses of 0.1 to 0.2 mg/kg, steady state peak plasma concentrations of lisinopril occurred within 6 hours and the extent of absorption based on urinary recovery was about 28%. These values are similar to those obtained previously in adults. The typical value of lisinopril oral clearance (systemic clearance/absolute bioavailability) in a child weighing 30 kg is 10 L/h, which increases in proportion to renal function.

Pharmacodynamics and Clinical Effects

Hypertension:

Adult Patients: Administration of PRINIVIL to patients with hypertension results in a reduction of 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 PRINIVIL, with peak reduction of blood pressure achieved by six 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 six hours after dosing.

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

The antihypertensive effects of PRINIVIL are maintained during long-term therapy. Abrupt withdrawal of PRINIVIL 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 PRINIVIL 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 PRINIVIL. In controlled clinical studies, PRINIVIL 20-80 mg has been compared in patients with mild to moderate hypertension to hydrochlorothiazide 12.5-50 mg and with atenolol 50-500 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 blood pressure in a population that was ¾ caucasian. PRINIVIL was approximately equivalent to atenolol and metoprolol in effects on diastolic blood pressure and had somewhat greater effects on systolic blood pressure.

PRINIVIL 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 nine hypertensive patients, following administration of PRINIVIL, 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 PRINIVIL 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 PRINIVIL has been shown to be well tolerated and effective in controlling blood pressure (see PRECAUTIONS).

Pediatric Patients: In a clinical study involving 115 hypertensive pediatric patients 6 to 16 years of age, patients who weighed <50 kg received either 0.625, 2.5, or 20 mg of lisinopril daily and patients who weighed ≥50 kg received either 1.25, 5, or 40 mg of lisinopril daily. At the end of 2 weeks, lisinopril administered once daily lowered trough blood pressure in a dose-dependent manner with consistent antihypertensive efficacy demonstrated at doses >1.25 mg (0.02 mg/kg). This effect was confirmed in a withdrawal phase, where the diastolic pressure rose by about 9 mmHg more in patients randomized to placebo than it did in patients who were randomized to remain on the middle and high doses of lisinopril. The dose-dependent antihypertensive effect of lisinopril was consistent across several demographic subgroups: age, Tanner stage, gender, race. In this study, lisinopril was generally well-tolerated.

In the above pediatric studies, lisinopril was given either as tablets or in a suspension for those children and infants who were unable to swallow tablets or who required a lower dose than is available in tablet form (see DOSAGE AND ADMINISTRATION, *Preparation of Suspension*).

Heart Failure: During baseline-controlled clinical trials, in patients receiving digitalis and diuretics, single doses of PRINIVIL resulted in decreases in pulmonary capillary wedge pressure, systemic vascular resistance and blood pressure accompanied by an increase in cardiac output and no change in heart rate.

In two placebo-controlled, 12-week clinical studies using doses of PRINIVIL up to 20 mg, PRINIVIL as adjunctive therapy to digitalis and diuretics improved the following signs and symptoms due to congestive heart failure: edema, rales, paroxysmal nocturnal dyspnea and jugular venous distention. In one of the studies beneficial response was also noted for: orthopnea, presence of third heart sound and the number of patients classified as NYHA Class III and IV. Exercise tolerance was also improved in this study. The effect of lisinopril on mortality in patients with heart failure has not been evaluated.

The once daily dosing for the treatment of congestive heart failure was the only dosage regimen used during clinical trial development and was determined by the measurement of hemodynamic responses.

Acute Myocardial Infarction: The Gruppo Italiano per lo Studio della Sopravvienza nell'Infarto Miocardico (GISSI - 3) study was a multicenter, controlled, randomized, unblinded clinical trial conducted in 19,394 patients with acute myocardial infarction admitted to a coronary care unit. It was designed to examine the effects of short-term (6 week) treatment with lisinopril, nitrates, their combination, or no therapy on short-term (6 week) mortality and on long-term death and markedly impaired cardiac function.

Patients presenting within 24 hours of the onset of symptoms who were hemodynamically stable were randomized, in a 2 x 2 factorial design, to six weeks of either

1) PRINIVIL alone (n = 4841),
2) nitrates alone (n = 4869),
3) PRINIVIL plus nitrates (n = 4841), or
4) open control (n = 4843).

All patients received routine therapies, including thrombolytics (72%), aspirin (84%), and a beta-blocker (31%), as appropriate, normally utilized in acute myocardial infarction (MI) patients.

The protocol excluded patients with hypotension (systolic blood pressure ≤100 mmHg), severe heart failure, cardiogenic shock and renal dysfunction (serum creatinine >2 mg/dL and/or proteinuria >500 mg/24 h). Doses of PRINIVIL were adjusted as necessary according to protocol. (See DOSAGE AND ADMINISTRATION.)

Study treatment was withdrawn at six weeks except where clinical conditions indicated continuation of treatment.

The primary outcomes of the trial were the overall mortality at six weeks and a combined endpoint at six months after the myocardial infarction, consisting of the number of patients who died, had late (day 4) clinical congestive heart failure, or had extensive left ventricular damage defined as ejection fraction ≤35%, or an akinetic-dyskinetic [A-D] score ≥45%. Patients receiving PRINIVIL (n = 9646) alone or with nitrates, had an 11 percent lower risk of death (2p [two-tailed] = 0.04) compared to patients receiving no PRINIVIL (n = 9672) (6.4 percent versus 7.2 percent, respectively) at six weeks. Although patients randomized to receive PRINIVIL for up to six weeks also fared numerically better on the combined end-point at 6 months, the open nature of the assessment of heart failure, substantial loss to follow-up echocardiography, and substantial excess use of lisinopril between 6 weeks and 6 months in the group randomized to 6 weeks of lisinopril, preclude any conclusion about this endpoint.

Patients with acute myocardial infarction, treated with PRINIVIL had a higher (9.0 percent versus 3.7 percent, respectively) incidence of persistent hypotension (systolic blood pressure <90 mmHg for more than 1 hour) and renal dysfunction (2.4 percent versus 1.1 percent) in-hospital and at six weeks (increasing creatinine concentration to over 3 mg/dL or a doubling or more of the baseline serum creatinine concentration). (See ADVERSE REACTIONS, *ACUTE MYOCARDIAL INFARCTION*.)

INDICATIONS AND USAGE

Hypertension

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

Heart Failure

PRINIVIL is indicated as adjunctive therapy in the management of heart failure in patients who are not responding adequately to diuretics and digitalis.

Acute Myocardial Infarction

PRINIVIL is indicated for the treatment of hemodynamically stable patients within 24 hours of acute myocardial infarction, to improve survival. Patients should receive, as appropriate, the standard recommended treatments such as thrombolytics, aspirin and beta-blockers.

In using PRINIVIL, 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 PRINIVIL does not have a similar risk. (See WARNINGS.)

In considering use of PRINIVIL, it should be noted that in controlled clinical trials ACE inhibitors have an effect on blood pressure that is less in Black patients than in non-Blacks. In addition, it should be noted that Black patients receiving ACE inhibitors have been reported to have a higher incidence of angioedema compared to non-Blacks (see WARNINGS, *Anaphylactoid and Possibly Related Reactions, Angioedema*).

CONTRAINDICATIONS

PRINIVIL 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 and in patients with hereditary or idiopathic angioedema.

WARNINGS

Anaphylactoid and Possibly Related Reactions

Presumably because angiotensin converting enzyme inhibitors affect the metabolism of eicosanoids and polypeptides, including endogenous bradykinin, patients receiving ACE inhibitors (including PRINIVIL) may be subject to a variety of adverse reactions, some of them serious.

Head and Neck Angioedema: Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with angiotensin converting enzyme inhibitors, including PRINIVIL. This may occur at any time during treatment. ACE inhibitors have been associated with a higher rate of angioedema in Black than in non-Black patients. In such cases PRINIVIL should be promptly discontinued and appropriate therapy and monitoring should be provided until complete and sustained resolution of signs and symptoms has occurred. 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, e.g., subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL) and/or measures necessary to ensure a patent airway, should be promptly provided.** (See ADVERSE REACTIONS.)

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see also INDICATIONS AND USAGE and CONTRAINDICATIONS).

Intestinal Angioedema: Intestinal angioedema has been reported in patients treated with ACE inhibitors. These patients presented with abdominal pain (with or without nausea or vomiting); in some cases there was no prior history of facial angioedema and C-1 esterase levels were normal. The angioedema was diagnosed by procedures including abdominal CT scan or ultrasound, or at surgery, and symptoms resolved after stopping the ACE inhibitor. Intestinal angioedema should be included in the differential diagnosis of patients on ACE inhibitors presenting with abdominal pain.

Anaphylactoid reactions during desensitization: Two patients undergoing desensitizing treatment with hymenoptera venom while receiving ACE inhibitors sustained life-threatening anaphylactoid reactions. In the same patients, these reactions were avoided when ACE inhibitors were temporarily withheld, but they reappeared upon inadvertent rechallenge.

Anaphylactoid reactions during membrane exposure: Sudden and potentially life-threatening anaphylactoid reactions have been reported in some patients dialyzed with high-flux membranes (e.g., AN69®) and treated concomitantly with an ACE inhibitor. In such patients, dialysis must be stopped immediately, and aggressive therapy for anaphylactoid reactions be initiated. Symptoms have not been relieved by antihistamines in these situations. In these patients, consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agent. Anaphylactoid reactions have also been reported in patients undergoing low-density lipoprotein apheresis with dextran sulfate absorption.

Hypotension

Excessive hypotension is rare in patients with uncomplicated hypertension treated with PRINIVIL alone.

Patients with heart failure given PRINIVIL commonly have some reduction in blood pressure with peak blood pressure reduction occurring 6 to 8 hours post dose, but discontinuation of therapy because of continuing symptomatic hypotension usually is not necessary when dosing instructions are followed; caution should be observed when initiating therapy. (See DOSAGE AND ADMINISTRATION.)

Patients at risk of excessive hypotension, sometimes associated with oliguria and/or progressive azotemia, and rarely with acute renal failure and/or death, include those with the following conditions or characteristics: heart failure with systolic blood pressure below 100 mmHg, hyponatremia, high dose diuretic therapy, recent intensive diuresis or increase in diuretic dose, renal dialysis, or severe volume

and/or salt depletion of any etiology. It may be advisable to eliminate the diuretic (except in patients with heart failure), reduce the diuretic dose or increase salt intake cautiously before initiating therapy with PRINIVIL in patients at risk for excessive hypotension who are able to tolerate such adjustments. (See PRECAUTIONS, *Drug Interactions*, and ADVERSE REACTIONS.)

Patients with acute myocardial infarction in the GISSI - 3 study had a higher (9.0 percent versus 3.7 percent) incidence of persistent hypotension (systolic blood pressure <90 mmHg for more than 1 hour) when treated with PRINIVIL. Treatment with PRINIVIL must not be initiated in acute myocardial infarction patients at risk of further serious hemodynamic deterioration after treatment with a vasodilator (e.g., systolic blood pressure of 100 mmHg or lower) or cardiogenic shock.

In patients at risk of excessive hypotension, therapy should be started under very close medical supervision and such patients should be followed closely for the first two weeks of treatment and whenever the dose of PRINIVIL and/or diuretic is increased. Similar considerations may apply to patients with ischemic heart or cerebrovascular disease, or in patients with acute myocardial infarction, in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

If excessive hypotension occurs, the patient should be placed in the supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses of PRINIVIL which usually can be given without difficulty once the blood pressure has stabilized. If symptomatic hypotension develops, a dose reduction or discontinuation of PRINIVIL or concomitant diuretic may be necessary.

Leukopenia/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 PRINIVIL are insufficient to show that PRINIVIL does not cause agranulocytosis at similar rates. Marketing experience has revealed rare cases of leukopenia/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.

Hepatic Failure

Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis, and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up.

Fetal/Neonatal Morbidity and Mortality

ACE inhibitors can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature. When pregnancy is detected, ACE inhibitors should be discontinued as soon as possible.

The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to the ACE-inhibitor exposure.

These adverse effects do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to ACE inhibitors only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should make every effort to discontinue the use of PRINIVIL as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to ACE inhibitors will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intraamniotic environment.

If oligohydramnios is observed, PRINIVIL should be discontinued unless it is considered lifesaving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure 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. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function. Lisinopril, which crosses the placenta, has been removed from neonatal circulation by peritoneal dialysis with some clinical benefit, and theoretically may be removed by exchange transfusion, although there is no experience with the latter procedure.

No teratogenic effects of lisinopril were seen in studies of pregnant mice, rats and rabbits. On a body surface area basis, the doses used were 55 times, 33 times, and 0.15 times, respectively, the maximum recommended human daily dose (MRHDD).

PRECAUTIONS

General

Aortic Stenosis/Hypertrophic Cardiomyopathy: As with all vasodilators, lisinopril should be given with caution to patients with obstruction in the outflow tract of the left ventricle.

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 PRINIVIL, 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 PRINIVIL and/or diuretic therapy. In such patients renal function should be monitored during the first few weeks of therapy.

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

Patients with acute myocardial infarction in the GISSI - 3 study, treated with PRINIVIL, had a higher (2.4 percent versus 1.1 percent) incidence of renal dysfunction in-hospital and at six weeks (increasing creatinine concentration to over 3 mg/dL or a doubling or more of the baseline serum creatinine concentration). In acute myocardial infarction, treatment with PRINIVIL should be initiated with caution in patients with evidence of renal dysfunction, defined as serum creatinine concentration exceeding 2 mg/dL. If renal dysfunction develops during treatment with PRINIVIL (serum creatinine concentration exceeding 3 mg/dL or a doubling from the pre-treatment value) then the physician should consider withdrawal of PRINIVIL.

Evaluation of patients with hypertension, heart failure, or myocardial infarction 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 percent of hypertensive patients and 4.8 percent of patients with 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 percent of hypertensive patients, 0.6 percent of patients with heart failure and 0.1 percent of patients with myocardial infarction. 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 PRINIVIL. (See *Drug Interactions*.)

Cough: Presumably due to the inhibition of the degradation of endogenous bradykinin, persistent nonproductive cough has been reported with all ACE inhibitors, always resolving after discontinuation of therapy. ACE inhibitor-induced cough should be considered in the differential diagnosis of cough.

Surgery/Anesthesia: In patients undergoing major surgery or during anesthesia with agents that produce hypotension, PRINIVIL 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 at any time during treatment with angiotensin converting enzyme inhibitors, including lisinopril. 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 patients 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.

Leukopenia/Neutropenia: Patients should be told to report promptly any indication of infection (e.g., sore throat, fever) which may be a sign of leukopenia/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 PRINIVIL 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 PRINIVIL. The possibility of hypotensive effects with PRINIVIL can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with PRINIVIL. If it is necessary to continue the diuretic, initiate therapy with PRINIVIL at a dose of 5 mg daily, and provide close medical supervision after the initial dose until blood pressure has stabilized. (See WARNINGS and DOSAGE AND ADMINISTRATION.) When a diuretic is added to the therapy of a patient receiving PRINIVIL, 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.)

Non-steroidal Anti-inflammatory Agents: In some patients with compromised renal function who are being treated with non-steroidal anti-inflammatory drugs, the co-administration of lisinopril may result in a further deterioration of renal function. These effects are usually reversible.

Reports suggest that NSAIDs may diminish the antihypertensive effect of ACE inhibitors, including lisinopril. This interaction should be given consideration in patients taking NSAIDs concomitantly with ACE inhibitors.

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

Other Agents: PRINIVIL has been used concomitantly with nitrates and/or digoxin without evidence of clinically significant adverse interactions. This included post myocardial infarction patients who were receiving intravenous or transdermal nitroglycerin. No clinically important pharmacokinetic interactions occurred when PRINIVIL was used concomitantly with propranolol or hydrochlorothiazide. The presence of food in the stomach does not alter the bioavailability of PRINIVIL.

Agents Increasing Serum Potassium: PRINIVIL attenuates potassium loss caused by thiazide-type diuretics. Use of PRINIVIL with potassium-sparing diuretics (e.g., 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. Potassium sparing agents should generally not be used in patients with heart failure who are receiving PRINIVIL.

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

Carcinogenesis, Mutagenesis, Impairment of Fertility

There was no evidence of a tumorigenic effect when lisinopril was administered orally for 105 weeks to male and female rats at doses up to 90 mg/kg/day or for 92 weeks to male and female mice at doses up to 135 mg/kg/day. These doses are 10 times and 7 times, respectively, the maximum recommended human daily dose (MRHDD) when compared on a body surface area basis.

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 (33 times the MRHDD when compared on a body surface area basis).

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 secreted in human milk. Because many drugs are secreted in human milk, and because of the potential for serious adverse reactions in nursing infants from ACE inhibitors, a decision should be made whether to discontinue nursing or discontinue PRINIVIL, taking into account the importance of the drug to the mother.

Pediatric Use

Antihypertensive effects of PRINIVIL have been established in hypertensive pediatric patients aged 6 to 16 years.

There are no data on the effect of PRINIVIL on blood pressure in pediatric patients under the age of 6 or in pediatric patients with glomerular filtration rate <30 mL/min/1.73 m^2 (see CLINICAL PHARMACOLOGY, *Pharmacokinetics and Metabolism* and *Pharmacodynamics and Clinical Effects,* and DOSAGE AND ADMINISTRATION).

Geriatric Use

Clinical studies of PRINIVIL in patients with hypertension and congestive heart failure did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other clinical experience in this population has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

In a clinical study of PRINIVIL in patients with myocardial infarctions 4413 (47 percent) were 65 and over, while 1656 (18 percent) were 75 and over. No overall differences in safety or efficacy were observed between elderly and younger patients.

Other reported clinical experience has not identified differences in responses between elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Pharmacokinetic studies indicate that maximum blood levels and area under plasma concentration time curve (AUC) are doubled in elderly patients.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection. Evaluation of patients with hypertension, congestive heart failure, or myocardial infarction should always include assessment of renal function. (See DOSAGE AND ADMINISTRATION.)

ADVERSE REACTIONS

PRINIVIL has been found to be generally well tolerated in controlled clinical trials involving 1969 patients with hypertension or heart failure. For the most part, adverse experiences were mild and transient.

HYPERTENSION

In clinical trials in patients with hypertension treated with PRINIVIL, discontinuation of therapy due to clinical adverse experiences occurred in 5.7 percent of patients. The overall frequency of adverse experiences could not be related to total daily dosage within the recommended therapeutic dosage range.

For adverse experiences occurring in greater than one percent of patients with hypertension treated with PRINIVIL or PRINIVIL plus hydrochlorothiazide in controlled clinical trials and more frequently with PRINIVIL and/or PRINIVIL plus hydrochlorothiazide than placebo, comparative incidence data are listed in the table below:

	Percent of Patients in Controlled Studies		
	PRINIVIL (n = 1349) Incidence (discontinuation)	PRINIVIL/ Hydrochlorothiazide (n = 629) Incidence (discontinuation)	Placebo (n = 207) Incidence (discontinuation)
Body As A Whole			
Fatigue	2.5 (0.3)	4.0 (0.5)	1.0 (0.0)
Asthenia	1.3 (0.5)	2.1 (0.2)	1.0 (0.0)
Orthostatic Effects	1.2 (0.0)	3.5 (0.2)	1.0 (0.0)
Cardiovascular			
Hypotension	1.2 (0.5)	1.6 (0.5)	0.5 (0.5)
Digestive			
Diarrhea	2.7 (0.2)	2.7 (0.3)	2.4 (0.0)
Nausea	2.0 (0.4)	2.5 (0.2)	2.4 (0.0)
Vomiting	1.1 (0.2)	1.4 (0.1)	0.5 (0.0)
Dyspepsia	0.9 (0.0)	1.9 (0.0)	0.0 (0.0)
Musculoskeletal			
Muscle Cramps	0.5 (0.0)	2.9 (0.8)	0.5 (0.0)
Nervous/Psychiatric			
Headache	5.7 (0.2)	4.5 (0.5)	1.9 (0.0)
Dizziness	5.4 (0.4)	9.2 (1.0)	1.9 (0.0)
Paresthesia	0.8 (0.1)	2.1 (0.2)	0.0 (0.0)
Decreased Libido	0.4 (0.1)	1.3 (0.1)	0.0 (0.0)
Vertigo	0.2 (0.1)	1.1 (0.2)	0.0 (0.0)
Respiratory			
Cough	3.5 (0.7)	4.6 (0.8)	1.0 (0.0)
Upper Respiratory Infection	2.1 (0.1)	2.7 (0.1)	0.0 (0.0)
Common Cold	1.1 (0.1)	1.3 (0.1)	0.0 (0.0)
Nasal Congestion	0.4 (0.1)	1.3 (0.1)	0.0 (0.0)
Influenza	0.3 (0.1)	1.1 (0.1)	0.0 (0.0)
Skin			
Rash	1.3 (0.4)	1.6 (0.2)	0.5 (0.5)
Urogenital			
Impotence	1.0 (0.4)	1.6 (0.5)	0.0 (0.0)

Chest pain and back pain were also seen but were more common on placebo than PRINIVIL.

HEART FAILURE

In patients with heart failure treated with PRINIVIL for up to four years, discontinuation of therapy due to clinical adverse experiences occurred in 11.0 percent of patients. In controlled studies in patients with heart failure, therapy was discontinued in 8.1 percent of patients treated with PRINIVIL for up to 12 weeks, compared to 7.7 percent of patients treated with placebo for 12 weeks.

The following table lists those adverse experiences which occurred in greater than one percent of patients with heart failure treated with PRINIVIL or placebo for up to 12 weeks in controlled clinical trials and more frequently on PRINIVIL than placebo.

	Controlled Trials	
	PRINIVIL (n=407) Incidence (discontinuation)	Placebo (n=155) Incidence (discontinuation)
	12 weeks	12 weeks
Body As A Whole		
Chest Pain	3.4 (0.2)	1.3 (0.0)
Abdominal Pain	2.2 (0.7)	1.9 (0.0)
Cardiovascular		
Hypotension	4.4 (1.7)	0.6 (0.6)
Digestive		
Diarrhea	3.7 (0.5)	1.9 (0.0)
Nervous/Psychiatric		
Dizziness	11.8 (1.2)	4.5 (1.3)
Headache	4.4 (0.2)	3.9 (0.0)
Respiratory		
Upper Respiratory Infection	1.5 (0.0)	1.3 (0.0)
Skin		
Rash	1.7 (0.5)	0.6 (0.6)

Also observed at >1% with PRINIVIL but more frequent or as frequent on placebo than PRINIVIL in controlled trials were asthenia, angina pectoris, nausea, dyspnea, cough and pruritus.

Worsening of heart failure, anorexia, increased salivation, muscle cramps, back pain, myalgia, depression, chest sound abnormalities and pulmonary edema were also seen in controlled clinical trials, but were more common on placebo than PRINIVIL.

ACUTE MYOCARDIAL INFARCTION

In the GISSI - 3 trial, in patients treated with PRINIVIL for six weeks following acute myocardial infarction, discontinuation of therapy occurred in 17.6 percent of patients.

Patients treated with PRINIVIL had a significantly higher incidence of hypotension and renal dysfunction compared with patients not taking PRINIVIL.

In the GISSI - 3 trial, hypotension (9.7 percent), renal dysfunction (2.0 percent), cough (0.5 percent), post-infarction angina (0.3 percent), skin rash and generalized edema (0.01 percent), and angioedema (0.01 percent) resulted in withdrawal of treatment. In elderly patients treated with PRINIVIL, discontinuation due to renal dysfunction was 4.2 percent.

Other clinical adverse experiences occurring in 0.3 to 1.0 percent of patients with hypertension or heart failure treated with PRINIVIL in 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 WARNINGS, *Anaphylactoid and Possibly Related Reactions*), syncope, orthostatic effects, chest discomfort, pain, pelvic pain, flank pain, edema, facial edema, virus infection, fever, chills, malaise.

Cardiovascular: Cardiac arrest; myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients (see WARNINGS, *Hypotension*); pulmonary embolism and infarction, arrhythmias (including ventricular tachycardia, atrial tachycardia, atrial fibrillation, bradycardia and premature ventricular contractions), palpitations, transient ischemic attacks, paroxysmal nocturnal dyspnea, orthostatic hypotension, decreased blood pressure, peripheral edema, vasculitis.

Digestive: Pancreatitis, hepatitis (hepatocellular or cholestatic jaundice) (see WARNINGS, *Hepatic Failure*), vomiting, gastritis, dyspepsia, heartburn, gastrointestinal cramps, constipation, flatulence, dry mouth.

Hematologic: Rare cases of bone marrow depression, hemolytic anemia, leukopenia/neutropenia, and thrombocytopenia.

Endocrine: Diabetes mellitus.

Metabolic: Weight loss, dehydration, fluid overload, gout, weight gain.

Musculoskeletal: Arthritis, arthralgia, neck pain, hip pain, low back pain, joint pain, leg pain, knee pain, shoulder pain, arm pain, lumbago.

Nervous System/Psychiatric: Stroke, ataxia, memory impairment, tremor, peripheral neuropathy (e.g., dysesthesia), spasm, paresthesia, confusion, insomnia, somnolence, hypersomnia, irritability, and nervousness.

Respiratory System: Malignant lung neoplasms, hemoptysis, pulmonary infiltrates, eosinophilic pneumonitis, bronchospasm, asthma, pleural effusion, pneumonia, bronchitis, wheezing, orthopnea, painful respiration, epistaxis, laryngitis, sinusitis, pharyngeal pain, pharyngitis, rhinitis, rhinorrhea.

Skin: Urticaria, alopecia, herpes zoster, photosensitivity, skin lesions, skin infections, pemphigus, erythema, flushing, diaphoresis. Other severe skin reactions (including toxic epidermal necrolysis and Stevens-Johnson syndrome) have been reported rarely; causal relationship has not been established.

Special Senses: Visual loss, diplopia, blurred vision, tinnitus, photophobia, taste disturbances.

Urogenital System: Acute renal failure, oliguria, anuria, uremia, progressive azotemia, renal dysfunction (see PRECAUTIONS and DOSAGE AND ADMINISTRATION), pyelonephritis, dysuria, urinary tract infection, breast pain.

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 PRINIVIL (0.1%) with an incidence higher in Black than in non-Black patients. Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis and/or larynx occurs, treatment with PRINIVIL should be discontinued and appropriate therapy instituted immediately. In rare cases, intestinal angioedema has been reported with angiotensin converting enzyme inhibitors including lisinopril. (See WARNINGS.)

Hypotension: In hypertensive patients, hypotension occurred in 1.2 percent and syncope occurred in 0.1 percent of patients. Hypotension or syncope was a cause for discontinuation of therapy in 0.5 percent of hypertensive patients. In patients with heart failure, hypotension occurred in 5.3 percent and syncope occurred in 1.8 percent of patients. These adverse experiences were causes for discontinuation of therapy in 1.8 percent of these patients. In patients treated with PRINIVIL for six weeks after acute myocardial infarction, hypotension (systolic blood pressure ≤100 mmHg) resulted in discontinuation of therapy in 9.7 percent of the patients. (See WARNINGS.)

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

Cough: See PRECAUTIONS, *Cough*.

Pediatric Patients: No relevant differences between the adverse experience profile for pediatric patients and that previously reported for adult patients were identified.

Clinical Laboratory Test Findings

Serum Electrolytes: Hyperkalemia (see PRECAUTIONS), hyponatremia.

Creatinine, Blood Urea Nitrogen: Minor increases in blood urea nitrogen and serum creatinine, reversible upon discontinuation of therapy, were observed in about 2.0 percent of patients with essential hypertension treated with PRINIVIL 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 11.6 percent of patients with 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 percent and 1.3 vol percent, respectively) occurred frequently in patients treated with PRINIVIL but were rarely of clinical importance in patients without some other cause of anemia. In clinical trials, less than 0.1 percent of patients discontinued therapy due to anemia. Hemolytic anemia has been reported; a causal relationship to lisinopril cannot be excluded.

Liver Function Tests: Rarely, elevations of liver enzymes and/or serum bilirubin have occurred (see WARNINGS, *Hepatic Failure*).

In hypertensive patients, 2.0 percent discontinued therapy due to laboratory adverse experiences, principally elevations in blood urea nitrogen (0.6 percent), serum creatinine (0.5 percent) and serum potassium (0.4 percent). In the heart failure trials, 3.4 percent of patients discontinued therapy due to laboratory adverse experiences, 1.8 percent due to elevations in blood urea nitrogen and/or creatinine and 0.6 percent due to elevations in serum potassium. In the myocardial infarction trial, 2.0 percent of patients receiving PRINIVIL discontinued therapy due to renal dysfunction (increasing creatinine concentration to over 3 mg/dL or a doubling or more of the baseline serum creatinine concentration); less than 1.0 percent

of patients discontinued therapy due to other laboratory adverse experiences: 0.1 percent with hyperkalemia and less than 0.1 percent with hepatic enzyme alterations.

OVERDOSAGE

Following a single oral dose of 20 g/kg, no lethality occurred in rats and death occurred in one of 20 mice receiving the same dose. 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. (See WARNINGS, *Anaphylactoid reactions during membrane exposure*.)

DOSAGE AND ADMINISTRATION

Hypertension

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 to 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 a greater effect. If blood pressure is not controlled with PRINIVIL 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 PRINIVIL.

Diuretic Treated Patients: In hypertensive patients who are currently being treated with a diuretic, symptomatic hypotension may occur occasionally following the initial dose of PRINIVIL. The diuretic should be discontinued, if possible, for two to three days before beginning therapy with PRINIVIL to reduce the likelihood of hypotension. (See WARNINGS.) The dosage of PRINIVIL should be adjusted according to blood pressure response. If the patient's blood pressure is not controlled with PRINIVIL 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 PRINIVIL with potassium supplements, potassium salt substitutes, or potassium-sparing diuretics may lead to increases of serum potassium (see PRECAUTIONS).

Dosage Adjustment in Renal Impairment: The usual dose of PRINIVIL (10 mg) is recommended for patients with a 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 mL/min	10 mg
Moderate to Severe Impairment	≥10 ≤30 mL/min	5 mg
Dialysis Patients**	<10 mL/min	2.5 mg***

** See WARNINGS, *Anaphylactoid reactions during membrane exposure*

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

Heart Failure

PRINIVIL is indicated as adjunctive therapy with diuretics and (usually) digitalis. The recommended starting dose is 5 mg once a day.

When initiating treatment with lisinopril in patients with heart failure, the initial dose should be administered under medical observation, especially in those patients with low blood pressure (systolic blood pressure below 100 mmHg). The mean peak blood pressure lowering occurs six to eight hours after dosing. Observation should continue until blood pressure is stable. The concomitant diuretic dose should be reduced, if possible, to help minimize hypovolemia which may contribute to hypotension. (See WARNINGS and PRECAUTIONS, *Drug Interactions*.) The appearance of hypotension after the initial dose of PRINIVIL does not preclude subsequent careful dose titration with the drug, following effective management of the hypotension.

The usual effective dosage range is 5 to 20 mg per day administered as a single daily dose.

Dosage Adjustment in Patients with Heart Failure and Renal Impairment or Hyponatremia: In patients with heart failure who have hyponatremia (serum sodium <130 mEq/L) or moderate to severe renal impairment (creatinine clearance ≤30 mL/min or serum creatinine >3 mg/dL), therapy with PRINIVIL should be initiated at a dose of 2.5 mg once a day under close medical supervision. (See WARNINGS and PRECAUTIONS, *Drug Interactions*.)

Acute Myocardial Infarction

In hemodynamically stable patients within 24 hours of the onset of symptoms of acute myocardial infarction, the first dose of PRINIVIL is 5 mg given orally, followed by 5 mg after 24 hours, 10 mg after 48 hours and then 10 mg of PRINIVIL once daily. Dosing should continue for six weeks. Patients should receive, as appropriate, the standard recommended treatments such as thrombolytics, aspirin and beta-blockers. Patients with a low systolic blood pressure (≤120 mmHg) when treatment is started or during the first 3 days after the infarct should be given a lower 2.5 mg oral dose of PRINIVIL (see WARNINGS). If hypotension occurs (systolic blood pressure ≤100 mmHg) a daily maintenance dose of 5 mg may be given with temporary reductions to 2.5 mg if needed. If prolonged hypotension occurs (systolic blood pressure <90 mmHg for more than 1 hour) PRINIVIL should be withdrawn. For patients who develop symptoms of heart failure, see DOSAGE AND ADMINISTRATION, *Heart Failure*.

Dosage Adjustment in Patients with Myocardial Infarction with Renal Impairment: In acute myocardial infarction, treatment with PRINIVIL should be initiated with caution in patients with evidence of renal dysfunction, defined as serum creatinine concentration exceeding 2 mg/dL. No evaluation of dosage adjustment in myocardial infarction patients with severe renal impairment has been performed.

Use in Elderly

In general, blood pressure response and adverse experiences were similar in younger and older patients given similar doses of PRINIVIL. 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.

Pediatric Hypertensive Patients ≥6 years of age

The usual recommended starting dose is 0.07 mg/kg once daily (up to 5 mg total). Dosage should be adjusted according to blood pressure response. Doses above 0.61 mg/kg (or in excess of 40 mg) have not been studied in pediatric patients. (See CLINICAL PHARMACOLOGY *Pharmacokinetics and Metabolism* and *Pharmacodynamics and Clinical Effects*.)

PRINIVIL is not recommended in pediatric patients <6 years or in pediatric patients with glomerular filtration rate <30 mL/min/1.73 m^2 (see CLINICAL PHARMACOLOGY, *Pharmacokinetics and Metabolism, Pharmacodynamics and Clinical Effects* and PRECAUTIONS).

Preparation of Suspension (for 200 mL of a 1.0 mg/mL suspension)

Add 10 mL of Purified Water USP to a polyethylene terephthalate (PET) bottle containing ten 20-mg tablets of PRINIVIL and shake for at least one minute. Add 30 mL of Bicitra®** diluent and 160 mL of Ora-Sweet SF™*** to the concentrate in the PET bottle and gently shake for several seconds to disperse the ingredients. The suspension should be stored at or below 25°C (77°F) and can be stored for up to four weeks. Shake the suspension before each use.

** Registered trademark of Alza Corporation
*** Trademark of Paddock Laboratories, Inc.

HOW SUPPLIED

No. 3658 — Tablets PRINIVIL, 2.5 mg, are white, round, flat-faced, beveled edge, compressed tablets, coded MSD on one side and 15 on the other. They are supplied as follows:

NDC 0006-0015-58 unit of use bottles of 100.

No. 3577 — Tablets PRINIVIL, 5 mg, are white, shield shaped, scored, compressed tablets, with code MSD 19 on one side and PRINIVIL on the other. They are supplied as follows:

NDC 0006-0019-54 unit of use bottles of 90

NDC 0006-0019-82 bottles of 1,000

NDC 0006-0019-87 bottles of 10,000.

No. 3578 — Tablets PRINIVIL, 10 mg, are light yellow, shield shaped, compressed tablets, with code MSD 106 on one side and PRINIVIL on the other. They are supplied as follows:

NDC 0006-0106-54 unit of use bottles of 90

NDC 0006-0106-82 bottles of 1,000

NDC 0006-0106-87 bottles of 10,000.

No. 3579 — Tablets PRINIVIL, 20 mg, are peach, shield shaped, compressed tablets, with code MSD 207 on one side and PRINIVIL on the other. They are supplied as follows:

NDC 0006-0207-54 unit of use bottles of 90

NDC 0006-0207-82 bottles of 1,000

NDC 0006-0207-87 bottles of 10,000.

No. 3580 — Tablets PRINIVIL, 40 mg, are rose red, shield shaped, compressed tablets, with code MSD 237 on one side and PRINIVIL on the other. They are supplied as follows:

NDC 0006-0237-58 unit of use bottles of 100.

Storage

Store at controlled room temperature, 15-30°C (59-86°F), and protect from moisture.

Dispense in a tight container, if product package is subdivided.

MERCK & CO., INC., Whitehouse Station, NJ 08889, USA

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