Merck Sharp & Dohme Corp., a subsidiary of
MERCK & CO., INC.
Whitehouse Station, NJ 08889, USA

TABLETS

PRINIVIL®

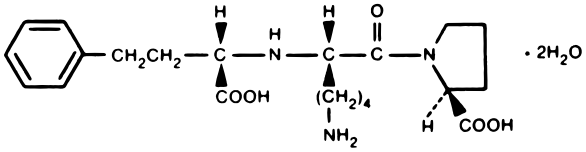
(LISINOPRIL)

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 5 mg, 10 mg, and 20 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 and 20 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.

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 Sopravvivenza 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, Head and Neck 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. Even in those instances where swelling of only the tongue is involved, without respiratory distress, patients may require prolonged observation since treatment with antihistamines and corticosteroids may not be sufficient. Very rarely, fatalities have been reported due to angioedema associated with laryngeal edema or tongue edema. Patients with involvement of the tongue, glottis or larynx are likely to experience airway obstruction, especially those with a history of airway surgery. **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 or hepatitis 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.

In a published retrospective epidemiological study, infants whose mothers had taken an ACE inhibitor drug during the first trimester of pregnancy appeared to have an increased risk of major congenital malformations compared with infants whose mothers had not undergone first trimester exposure to ACE inhibitor drugs. The number of cases of birth defects is small and the findings of this study have not yet been repeated.

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. Hyperkalemia can cause serious, sometimes fatal, arrhythmias. PRINIVIL should be used cautiously, if at all, with these agents and with frequent monitoring of serum potassium. (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.

Hypoglycemia: Diabetic patients treated with oral antidiabetic agents or insulin starting an ACE inhibitor should be told to closely monitor for hypoglycemia, especially during the first month of combined use. (See *Drug Interactions*.)

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 exposure to ACE inhibitors during pregnancy. 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.)

Antidiabetics: Epidemiological studies have suggested that concomitant administration of ACE inhibitors and antidiabetic medicines (insulins, oral hypoglycemic agents) may cause an increased blood-glucose-lowering effect with risk of hypoglycemia. This phenomenon appeared to be more likely to occur during the first weeks of combined treatment and in patients with renal impairment. In diabetic patients treated with oral antidiabetic agents or insulin, glycemic control should be closely monitored for hypoglycemia, especially during the first month of treatment with an ACE inhibitor.

Non-steroidal Anti-inflammatory Agents Including Selective Cyclooxygenase-2 (COX-2) Inhibitors: Reports suggest that NSAIDs including selective COX-2 inhibitors may diminish the antihypertensive effect of ACE inhibitors, including lisinopril. This interaction should be given consideration in patients taking NSAIDs or selective COX-2 inhibitors 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.

In some patients with compromised renal function (e.g., elderly patients or patients who are volume-depleted including those on diuretic therapy) who are being treated with non-steroidal anti-inflammatory drugs, including selective COX-2 inhibitors, the co-administration of angiotensin II receptor antagonists or ACE inhibitors may result in a further deterioration of renal function, including possible acute renal failure. These effects are usually reversible.

These interactions should be considered in patients taking NSAIDS including selective COX-2 inhibitors concomitantly with diuretics and angiotensin II antagonists or ACE inhibitors. Therefore, monitor effects on blood pressure and renal function when administering the combination, especially in the elderly.

Dual Blockade of the Renin-angiotensin-aldosterone System: Dual blockade of the renin-angiotensin-aldosterone system: Dual blockade of the renin-angiotensin-aldosterone system is associated with increased risk of hypotension, syncope, hyperkalemia, and changes in renal function (including acute renal failure). Closely monitor blood pressure, renal function and electrolytes in patients on Prinivil and angiotensin receptor blockers.

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, eplerenone, 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.

Gold: Nitritoid reactions (symptoms include facial flushing, nausea, vomiting and hypotension) have been reported rarely in patients on therapy with injectable gold (sodium aurothiomalate) and concomitant ACE inhibitor therapy including PRINIVIL.

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, syndrome of inappropriate antidiuretic hormone secretion (SIADH).

Metabolic: Weight loss, dehydration, fluid overload, gout, weight gain. Cases of hypoglycemia in diabetic patients on oral antidiabetic agents or insulin have been reported (see PRECAUTIONS, *Drug Interactions*).

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, Stevens-Johnson syndrome and cutaneous pseudolymphoma) 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.

HOW SUPPLIED

No. 8110 — Tablets PRINIVIL, 5 mg, are white, oval shaped compressed tablets with code MSD 19 on one side and scored on the other side. They are supplied as follows:

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

No. 8111 — Tablets PRINIVIL, 10 mg, are light yellow, oval shaped compressed tablets with code MSD 106 on one side and scored on the other side. They are supplied as follows:

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

No. 8112 — Tablets PRINIVIL, 20 mg, are peach, oval shaped compressed tablets with code MSD 207 on one side and scored on the other side. They are supplied as follows:

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

Storage

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

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

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

Manuf. for: Merck Sharp & Dohme Corp., a subsidiary of
MERCK & CO., INC., Whitehouse Station, NJ 08889, USA

by:

MERCK SHARP & DOHME LTD.
Cramlington, Northumberland, UK NE23 3JU

Issued June 2011

Merck Sharp & Dohme Corp., a subsidiary of
MERCK & CO., INC.
Whitehouse Station, NJ 08889, USA

TABLETS

PRINZIDE®

(LISINOPRIL-HYDROCHLOROTHIAZIDE)

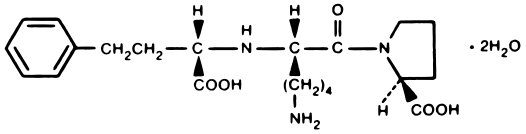
USE IN PREGNANCY

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, PRINZIDE should be discontinued as soon as possible. See WARNINGS, *Pregnancy, Lisinopril, Fetal/Neonatal Morbidity and Mortality*.

DESCRIPTION

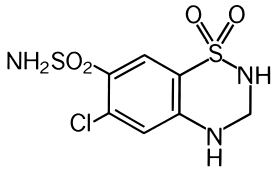
PRINZIDE® (Lisinopril-Hydrochlorothiazide) combines an angiotensin converting enzyme inhibitor, lisinopril, and a diuretic, hydrochlorothiazide.

Lisinopril, a synthetic peptide derivative, is an oral long-acting angiotensin converting enzyme inhibitor. It 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, sparingly soluble in methanol, and practically insoluble in ethanol.

Hydrochlorothiazide is 6-chloro-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide. Its empirical formula is $C_7H_8ClN_3O_4S_2$ and its structural formula is:



Hydrochlorothiazide is a white, or practically white, crystalline powder with a molecular weight of 297.73, which is slightly soluble in water, but freely soluble in sodium hydroxide solution.

PRINZIDE is available for oral use in two tablet combinations of lisinopril with hydrochlorothiazide: PRINZIDE 10-12.5, containing 10 mg lisinopril and 12.5 mg hydrochlorothiazide and PRINZIDE 20-12.5, containing 20 mg lisinopril and 12.5 mg hydrochlorothiazide.

Inactive ingredients are calcium phosphate, magnesium stearate, mannitol, and starch. PRINZIDE 10-12.5 also contains FD&C Blue #2 aluminum lake. PRINZIDE 20-12.5 also contains iron oxide.

CLINICAL PHARMACOLOGY

Lisinopril-Hydrochlorothiazide

As a result of its diuretic effects, hydrochlorothiazide increases plasma renin activity, increases aldosterone secretion, and decreases serum potassium. Administration of lisinopril blocks the renin-angiotensin-aldosterone axis and tends to reverse the potassium loss associated with the diuretic.

In clinical studies, the extent of blood pressure reduction seen with the combination of lisinopril and hydrochlorothiazide was approximately additive. The PRINZIDE 10-12.5 combination worked equally well in Black and Caucasian patients. The PRINZIDE 20-12.5 and PRINZIDE 20-25 (a previously - marketed strength) combinations appeared somewhat less effective in Black patients, but relatively few Black

patients were studied. In most patients, the antihypertensive effect of PRINZIDE was sustained for at least 24 hours.

In a randomized, controlled comparison, the mean antihypertensive effects of PRINZIDE 20-12.5 and PRINZIDE 20-25 were similar, suggesting that many patients who respond adequately to the latter combination may be controlled with PRINZIDE 20-12.5. (See DOSAGE AND ADMINISTRATION.)

Concomitant administration of lisinopril and hydrochlorothiazide has little or no effect on the bioavailability of either drug. The combination tablet is bioequivalent to concomitant administration of the separate entities.

Lisinopril

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. Removal of angiotensin II negative feedback on renin secretion leads to increased plasma renin activity. In hypertensive patients with normal renal function treated with lisinopril alone for up to 24 weeks, the mean increase in serum potassium was less than 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 lisinopril plus a thiazide diuretic showed essentially no change in serum potassium. (See PRECAUTIONS.)

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 lisinopril remains to be elucidated.

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

Pharmacokinetics and Metabolism

Following oral administration of lisinopril, peak serum concentrations 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 percent, with large intersubject 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.

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. However, 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.

Pharmacodynamics

Administration of lisinopril 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.)

In most patients studied, onset of antihypertensive activity was seen at one hour after oral administration of an individual dose of lisinopril, with peak reduction of blood pressure achieved by six hours.

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

At recommended single daily doses, antihypertensive effects have been maintained for at least 24 hours after dosing, although the effect at 24 hours was substantially smaller than the effect six hours after dosing.

The antihypertensive effects of lisinopril have continued during long-term therapy. Abrupt withdrawal of lisinopril has not been associated with a rapid increase in blood pressure; nor with a significant overshoot of pretreatment blood pressure.

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 lisinopril, 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 lisinopril has been shown to be well tolerated and effective in controlling blood pressure (see PRECAUTIONS).

Hydrochlorothiazide

The mechanism of the antihypertensive effect of thiazides is unknown. Thiazides do not usually affect normal blood pressure.

Hydrochlorothiazide is a diuretic and antihypertensive. It affects the distal renal tubular mechanism of electrolyte reabsorption. Hydrochlorothiazide increases excretion of sodium and chloride in approximately equivalent amounts. Natriuresis may be accompanied by some loss of potassium and bicarbonate.

After oral use diuresis begins within two hours, peaks in about four hours and lasts about 6 to 12 hours.

Hydrochlorothiazide is not metabolized but is eliminated rapidly by the kidney. When plasma levels have been followed for at least 24 hours, the plasma half-life has been observed to vary between 5.6 and 14.8 hours. At least 61 percent of the oral dose is eliminated unchanged within 24 hours. Hydrochlorothiazide crosses the placental but not the blood-brain barrier.

INDICATIONS AND USAGE

PRINZIDE is indicated for the treatment of hypertension.

These fixed-dose combinations are not indicated for initial therapy (see DOSAGE AND ADMINISTRATION).

In using PRINZIDE, consideration should be given to the fact that an 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 lisinopril does not have a similar risk. (See WARNINGS.)

In considering use of PRINZIDE, 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, *Head and Neck Angioedema*.)

CONTRAINDICATIONS

PRINZIDE is contraindicated in patients who are hypersensitive to any component of 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. Because of the hydrochlorothiazide component, this product is contraindicated in patients with anuria or hypersensitivity to other sulfonamide-derived drugs.

WARNINGS

General

Lisinopril

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 PRINZIDE) 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 rarely in patients treated with angiotensin converting enzyme inhibitors, including lisinopril. 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 PRINZIDE should be promptly discontinued and appropriate therapy and monitoring should be provided until complete and sustained resolution of signs and symptoms has occurred. Even in those instances where swelling of only the tongue is involved, without respiratory distress, patients may require prolonged observation since treatment with antihistamines and corticosteroids may not be sufficient. Very rarely, fatalities have been reported due to angioedema associated with laryngeal edema or tongue edema. Patients with involvement of the tongue, glottis or larynx are likely to experience airway obstruction, especially those with a history of airway surgery. **Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, 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: Anaphylactoid reactions have been reported in patients dialyzed with high-flux membranes and treated concomitantly with an ACE inhibitor. Anaphylactoid reactions have also been reported in patients undergoing low-density lipoprotein apheresis with dextran sulfate absorption.

Hypotension and Related Effects

Excessive hypotension was rarely seen in uncomplicated hypertensive patients but is a possible consequence of lisinopril use in salt/volume-depleted persons, such as those treated vigorously with diuretics or patients on dialysis. (See PRECAUTIONS, *Drug Interactions* and ADVERSE REACTIONS.)

Syncope has been reported in 0.8 percent of patients receiving PRINZIDE. In patients with hypertension receiving lisinopril alone, the incidence of syncope was 0.1 percent. The overall incidence of syncope may be reduced by proper titration of the individual components. (See PRECAUTIONS, *Drug Interactions*, ADVERSE REACTIONS and DOSAGE AND ADMINISTRATION.)

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 lisinopril 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 lisinopril are insufficient to show that lisinopril 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.

Hepatic Failure

Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice or hepatitis 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.

Hydrochlorothiazide

Thiazides should be used with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function.

Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma.

The possibility of exacerbation or activation of systemic lupus erythematosus has been reported.

Lithium generally should not be given with thiazides (see PRECAUTIONS, *Drug Interactions, Lisinopril* and *Hydrochlorothiazide*).

Pregnancy

Lisinopril-Hydrochlorothiazide

Teratogenicity studies were conducted in mice and rats with up to 90 mg/kg/day of lisinopril in combination with 10 mg/kg/day of hydrochlorothiazide. This dose of lisinopril is 5 times (in mice) and 10 times (in rats) the maximum recommended human daily dose (MRHDD) when compared on a body surface area basis (mg/m^2); the dose of hydrochlorothiazide is 0.9 times (in mice) and 1.8 times (in rats) the MRHDD. Maternal or fetotoxic effects were not seen in mice with the combination. In rats decreased maternal weight gain and decreased fetal weight occurred down to 3/10 mg/kg/day (the lowest dose tested). Associated with the decreased fetal weight was a delay in fetal ossification. The decreased fetal weight and delay in fetal ossification were not seen in saline-supplemented animals given 90/10 mg/kg/day.

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, PRINZIDE should be discontinued as soon as possible. (See *Lisinopril, Fetal/Neonatal Morbidity and Mortality*, below.)

Lisinopril

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.

In a published retrospective epidemiological study, infants whose mothers had taken an ACE inhibitor drug during the first trimester of pregnancy appeared to have an increased risk of major congenital malformations compared with infants whose mothers had not undergone first trimester exposure to ACE inhibitor drugs. The number of cases of birth defects is small and the findings of this study have not yet been repeated.

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 PRINZIDE 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, PRINZIDE 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 up 55 times, 33 times, and 0.15 times, respectively, the MRHDD.

Hydrochlorothiazide

Studies in which hydrochlorothiazide was orally administered to pregnant mice and rats during their respective periods of major organogenesis at doses up to 3000 and 1000 mg/kg/day, respectively, provided no evidence of harm to the fetus. These doses are more than 150 times the MRHDD on a body surface area basis. Thiazides cross the placental barrier and appear in cord blood. There is a risk of fetal or neonatal jaundice, thrombocytopenia and possibly other adverse reactions that have occurred in adults.

PRECAUTIONS

General

Lisinopril

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 lisinopril, 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 lisinopril 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 and serum creatinine, usually minor and transient, especially when lisinopril has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction of lisinopril and/or discontinuation of the diuretic may be required.

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

Hyperkalemia: In clinical trials hyperkalemia (serum potassium greater than 5.7 mEq/L) occurred in approximately 1.4 percent of hypertensive patients treated with lisinopril plus hydrochlorothiazide. In most cases these were isolated values which resolved despite continued therapy. Hyperkalemia was not a cause of discontinuation of therapy. 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. Hyperkalemia can cause serious, sometimes fatal, arrhythmias. PRINZIDE should be used cautiously, if at all, with these agents and with frequent monitoring of serum potassium. (See PRECAUTIONS, *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, lisinopril 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.

Hydrochlorothiazide

Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals.

All patients receiving thiazide therapy should be observed for clinical signs of fluid or electrolyte imbalance: namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Warning signs or symptoms of fluid and electrolyte imbalance, irrespective of cause, include dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, confusion, seizures, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

Hypokalemia may develop, especially with brisk diuresis, when severe cirrhosis is present, or after prolonged therapy.

Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia may cause cardiac arrhythmia and may also sensitize or exaggerate the response of the heart to the toxic effects of digitalis (e.g., increased ventricular irritability). Because lisinopril reduces the production of aldosterone, concomitant therapy with lisinopril attenuates the diuretic-induced potassium loss (see PRECAUTIONS, *Drug Interactions, Agents Increasing Serum Potassium*).

Although any chloride deficit is generally mild and usually does not require specific treatment, except under extraordinary circumstances (as in liver disease or renal disease), chloride replacement may be required in the treatment of metabolic alkalosis.

Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt except in rare instances when the hyponatremia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy.

In diabetic patients dosage adjustments of insulin or oral hypoglycemic agents may be required. Hyperglycemia may occur with thiazide diuretics. Thus latent diabetes mellitus may become manifest during thiazide therapy.

The antihypertensive effects of the drug may be enhanced in the postsympathectomy patient.

If progressive renal impairment becomes evident consider withholding or discontinuing diuretic therapy.

Thiazides have been shown to increase the urinary excretion of magnesium; this may result in hypomagnesemia.

Thiazides may decrease urinary calcium excretion. Thiazides may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy.

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.

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

Pregnancy: Female patients of childbearing age should be told about the consequences of exposure to ACE inhibitors during pregnancy. 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 PRINZIDE 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

Lisinopril

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 lisinopril. The possibility of hypotensive effects with lisinopril can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with lisinopril. If it is necessary to continue the diuretic, initiate therapy with lisinopril 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 lisinopril, an additional antihypertensive effect is usually observed. (See DOSAGE AND ADMINISTRATION.)

Non-steroidal Anti-inflammatory Agents Including Selective Cyclooxygenase-2 (COX-2) Inhibitors: Reports suggest that NSAIDs including selective COX-2 inhibitors may diminish the antihypertensive effect of ACE inhibitors, including lisinopril. This interaction should be given consideration in patients taking NSAIDs or selective COX-2 inhibitors concomitantly with ACE inhibitors.

In some patients with compromised renal function (e.g., elderly patients or patients who are volume-depleted, including those on diuretic therapy) who are being treated with non-steroidal anti-inflammatory drugs, including selective COX-2 inhibitors, the co-administration of angiotensin II receptor antagonists or ACE inhibitors, may result in a further deterioration of renal function, including possible acute renal failure. These effects are usually reversible.

These interactions should be considered in patients taking NSAIDS including selective COX-2 inhibitors concomitantly with diuretics and angiotensin II antagonists or ACE inhibitors. Therefore, monitor

effects on blood pressure and renal function when administering the combination, especially in the elderly.

Dual Blockade of the Renin-angiotensin-aldosterone System: Dual blockade of the renin-angiotensin-aldosterone system: Dual blockade of the renin-angiotensin-aldosterone system is associated with increased risk of hypotension, syncope, hyperkalemia, and changes in renal function (including acute renal failure). Closely monitor blood pressure, renal function and electrolytes in patients on Prinivil and angiotensin receptor blockers.

Other Agents: Lisinopril has been used concomitantly with nitrates and/or digoxin without evidence of clinically significant adverse interactions. No meaningful clinically important pharmacokinetic interactions occurred when lisinopril was used concomitantly with propranolol, digoxin, or hydrochlorothiazide. The presence of food in the stomach does not alter the bioavailability of lisinopril.

Agents Increasing Serum Potassium: Lisinopril attenuates potassium loss caused by thiazide-type diuretics. Use of lisinopril with potassium-sparing diuretics (e.g., spironolactone, eplerenone, 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 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 lisinopril is administered concomitantly with lithium.

Gold: Nitritoid reactions (symptoms include facial flushing, nausea, vomiting and hypotension) have been reported rarely in patients on therapy with injectable gold (sodium aurothiomalate) and concomitant ACE inhibitor therapy including PRINZIDE.

Hydrochlorothiazide

When administered concurrently the following drugs may interact with thiazide diuretics.

Alcohol, barbiturates, or narcotics — potentiation of orthostatic hypotension may occur.

Antidiabetic drugs (oral agents and insulin) — dosage adjustment of the antidiabetic drug may be required.

Other antihypertensive drugs — additive effect or potentiation.

Cholestyramine and colestipol resins — Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85 and 43 percent, respectively.

Corticosteroids, ACTH — intensified electrolyte depletion, particularly hypokalemia.

Pressor amines (e.g., norepinephrine) — possible decreased response to pressor amines but not sufficient to preclude their use.

Skeletal muscle relaxants, nondepolarizing (e.g., tubocurarine) — possible increased responsiveness to the muscle relaxant.

Lithium — should not generally be given with diuretics. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity. Refer to the package insert for lithium preparations before use of such preparations with PRINZIDE.

Non-steroidal Anti-inflammatory Drugs — In some patients, the administration of a non-steroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing and thiazide diuretics. Therefore, when PRINZIDE and non-steroidal anti-inflammatory agents are used concomitantly, the patient should be observed closely to determine if the desired effect of PRINZIDE is obtained.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Lisinopril-Hydrochlorothiazide

Lisinopril in combination with hydrochlorothiazide was not mutagenic in a microbial mutagen test using *Salmonella typhimurium* (Ames test) or *Escherichia coli* with or without metabolic activation or in a forward mutation assay using Chinese hamster lung cells. Lisinopril-hydrochlorothiazide did not produce DNA single strand breaks in an *in vitro* alkaline elution rat hepatocyte assay. In addition, it 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.

Lisinopril

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).

Hydrochlorothiazide

Two-year feeding studies in mice and rats conducted under the auspices of the National Toxicology Program (NTP) uncovered no evidence of a carcinogenic potential of hydrochlorothiazide in female mice at doses of up to approximately 600 mg/kg/day (53 times the MRHDD when compared on a body surface area basis) or in male and female rats at doses of up to approximately 100 mg/kg/day (18 times the MRHDD when compared on a body surface area basis). The NTP, however, found equivocal evidence for hepatocarcinogenicity in male mice.

Hydrochlorothiazide was not genotoxic *in vitro* in the Ames mutagenicity assay of *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538 and in the Chinese Hamster Ovary (CHO) test for chromosomal aberrations, or *in vivo* in assays using mouse germinal cell chromosomes, Chinese hamster bone marrow chromosomes, and the *Drosophila* sex-linked recessive lethal trait gene. Positive test results were obtained only in the *in vitro* CHO Sister Chromatid Exchange (clastogenicity) and in the Mouse Lymphoma Cell (mutagenicity) assays, using concentrations of hydrochlorothiazide from 43 to 1300 μg/mL, and in the *Aspergillus nidulans* non-disjunction assay at an unspecified concentration.

Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sex in studies wherein these species were exposed, via their diet, to doses of up to 100 and 4 mg/kg, respectively, prior to conception and throughout gestation. In mice and rats these doses are 9 times and 0.7 times, respectively, the MRHDD when compared on a body surface area basis.

Pregnancy

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

Nursing Mothers

It is not known whether lisinopril is secreted in human milk. However, milk of lactating rats contains radioactivity following administration of ^{14}C lisinopril. In another study, lisinopril was present in rat milk at levels similar to plasma levels in the dams. Thiazides do appear in human milk. Because of the potential for serious reactions in nursing infants from ACE inhibitors and hydrochlorothiazide, a decision should be made whether to discontinue nursing or to discontinue PRINZIDE, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Clinical studies of PRINZIDE did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience 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 multiple-dose pharmacokinetic study in elderly versus young hypertensive patients using the lisinopril/hydrochlorothiazide combination, area under the plasma

concentration time curve (AUC) increased approximately 120% for lisinopril and approximately 80% for hydrochlorothiazide in older 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 the hypertensive patient should always include assessment of renal function. (See DOSAGE AND ADMINISTRATION.)

ADVERSE REACTIONS

PRINZIDE has been evaluated for safety in 930 patients, including 100 patients treated for 50 weeks or more.

In clinical trials with PRINZIDE no adverse experiences peculiar to this combination drug have been observed. Adverse experiences that have occurred have been limited to those that have been previously reported with lisinopril or hydrochlorothiazide.

The most frequent clinical adverse experiences in controlled trials (including open label extensions) with any combination of lisinopril and hydrochlorothiazide were: dizziness (7.5 percent), headache (5.2 percent), cough (3.9 percent), fatigue (3.7 percent) and orthostatic effects (3.2 percent), all of which were more common than in placebo-treated patients. Generally, adverse experiences were mild and transient in nature; but see WARNINGS regarding angioedema and excessive hypotension or syncope. Discontinuation of therapy due to adverse effects was required in 4.4 percent of patients, principally because of dizziness, cough, fatigue and muscle cramps.

Adverse experiences occurring in greater than one percent of patients treated with lisinopril plus hydrochlorothiazide in controlled clinical trials are shown below.

	Percent of Patients in Controlled Studies	
	Lisinopril-Hydrochlorothiazide (n=930) Incidence (discontinuation)	Placebo (n=207) Incidence
Dizziness	7.5 (0.8)	1.9
Headache	5.2 (0.3)	1.9
Cough	3.9 (0.6)	1.0
Fatigue	3.7 (0.4)	1.0
Orthostatic Effects	3.2 (0.1)	1.0
Diarrhea	2.5 (0.2)	2.4
Nausea	2.2 (0.1)	2.4
Upper Respiratory Infection	2.2 (0.0)	0.0
Muscle Cramps	2.0 (0.4)	0.5
Asthenia	1.8 (0.2)	1.0
Paresthesia	1.5 (0.1)	0.0
Hypotension	1.4 (0.3)	0.5
Vomiting	1.4 (0.1)	0.5
Dyspepsia	1.3 (0.0)	0.0
Rash	1.2 (0.1)	0.5
Impotence	1.2 (0.3)	0.0

Clinical adverse experiences occurring in 0.3 to 1.0 percent of patients in controlled trials included: *Body as a Whole:* Chest pain, abdominal pain, syncope, chest discomfort, fever, trauma, virus infection. *Cardiovascular:* Palpitation, orthostatic hypotension. *Digestive:* Gastrointestinal cramps, dry mouth, constipation, heartburn. *Musculoskeletal:* Back pain, shoulder pain, knee pain, back strain, myalgia, foot pain. *Nervous/Psychiatric:* Decreased libido, vertigo, depression, somnolence. *Respiratory:* Common cold, nasal congestion, influenza, bronchitis, pharyngeal pain, dyspnea, pulmonary congestion, chronic sinusitis, allergic rhinitis, pharyngeal discomfort. *Skin:* Flushing, pruritus, skin inflammation, diaphoresis. *Special Senses:* Blurred vision, tinnitus, otalgia. *Urogenital:* Urinary tract infection.

Angioedema: Angioedema has been reported in patients receiving PRINZIDE, 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 PRINZIDE 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 clinical trials, adverse effects relating to hypotension occurred as follows: hypotension (1.4), orthostatic hypotension (0.5), other orthostatic effects (3.2). In addition syncope occurred in 0.8 percent of patients. (See WARNINGS.)

Cough: See PRECAUTIONS, *Cough*.

Clinical Laboratory Test Findings

Serum Electrolytes: See PRECAUTIONS.

Creatinine, Blood Urea Nitrogen: Minor reversible increases in blood urea nitrogen and serum creatinine were observed in patients with essential hypertension treated with PRINZIDE. More marked increases have also been reported and were more likely to occur in patients with renal artery stenosis. (See PRECAUTIONS.)

Serum Uric Acid, Glucose, Magnesium, Cholesterol, Triglycerides and Calcium: See PRECAUTIONS.

Hemoglobin and Hematocrit: Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.5 g percent and 1.5 vol percent, respectively) occurred frequently in hypertensive patients treated with PRINZIDE but were rarely of clinical importance unless another cause of anemia coexisted. In clinical trials, 0.4 percent of patients discontinued therapy due to anemia.

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

Other adverse reactions that have been reported with the individual components are listed below:

Lisinopril — In clinical trials adverse reactions which occurred with lisinopril were also seen with PRINZIDE. In addition, and since lisinopril has been marketed, the following adverse reactions have been reported with lisinopril and should be considered potential adverse reactions for PRINZIDE: *Body as a Whole:* Anaphylactoid reactions (see WARNINGS, *Anaphylactoid and Possibly Related Reactions*), malaise, edema, facial edema, pain, pelvic pain, flank pain, chills; *Cardiovascular:* Cardiac arrest, myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high-risk patients (see WARNINGS, *Hypotension*), pulmonary embolism and infarction, worsening of heart failure, arrhythmias (including tachycardia, ventricular tachycardia, atrial tachycardia, atrial fibrillation, bradycardia, and premature ventricular contractions), angina pectoris, transient ischemic attacks, paroxysmal nocturnal dyspnea, decreased blood pressure, peripheral edema, vasculitis; *Digestive:* Pancreatitis, hepatitis (hepatocellular or cholestatic jaundice) (see WARNINGS, *Hepatic Failure*), gastritis, anorexia, flatulence, increased salivation; *Endocrine:* Diabetes mellitus, syndrome of inappropriate antidiuretic hormone secretion (SIADH); *Hematologic:* Rare cases of neutropenia, thrombocytopenia, and bone marrow depression have been reported. Hemolytic anemia has been reported; a causal relationship to lisinopril cannot be excluded; *Metabolic:* Gout, weight loss, dehydration, fluid overload, weight gain; *Musculoskeletal:* Arthritis, arthralgia, neck pain, hip pain, joint pain, leg pain, arm pain, lumbago; *Nervous System/Psychiatric:* Ataxia, memory impairment, tremor, insomnia, stroke, nervousness, confusion, peripheral neuropathy (e.g., paresthesia, dysesthesia), spasm, hypersomnia, irritability; *Respiratory:* Malignant lung neoplasms, hemoptysis, pulmonary edema, pulmonary infiltrates, eosinophilic pneumonitis, bronchospasm, asthma, pleural effusion, pneumonia, wheezing, orthopnea, painful respiration, epistaxis, laryngitis, sinusitis, pharyngitis, rhinitis, rhinorrhea, chest sound abnormalities; *Skin:* Urticaria, alopecia, herpes zoster, photosensitivity, skin lesions, skin infections, pemphigus, erythema. Other severe skin reactions (including toxic epidermal necrolysis, Stevens-Johnson syndrome and cutaneous pseudolymphoma) have been reported rarely; causal relationship has not been established; *Special Senses:* Visual loss, diplopia, photophobia, taste disturbances; *Urogenital:* Acute renal failure, oliguria, anuria, uremia, progressive azotemia, renal dysfunction (see PRECAUTIONS and DOSAGE AND ADMINISTRATION), pyelonephritis, dysuria, 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, leukocytosis, eosinophilia, photosensitivity, rash, and other dermatological manifestations.

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

Hydrochlorothiazide — Body as a Whole: Weakness; *Digestive:* Anorexia, gastric irritation, cramping, jaundice (intrahepatic cholestatic jaundice), pancreatitis, sialadenitis, constipation; *Hematologic:* Leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia, hemolytic anemia; *Musculoskeletal:* Muscle spasm; *Nervous System/Psychiatric:* Restlessness; *Renal:* Renal failure, renal dysfunction, interstitial nephritis (see WARNINGS); *Skin:* Erythema multiforme including Stevens-Johnson syndrome, exfoliative dermatitis including toxic epidermal necrolysis, alopecia; *Special Senses:* Xanthopsia; *Hypersensitivity:* Purpura, photosensitivity, urticaria, necrotizing angiitis (vasculitis and cutaneous vasculitis), respiratory distress including pneumonitis and pulmonary edema, anaphylactic reactions.

OVERDOSAGE

No specific information is available on the treatment of overdosage with PRINZIDE. Treatment is symptomatic and supportive. Therapy with PRINZIDE should be discontinued and the patient observed closely. Suggested measures include induction of emesis and/or gastric lavage, and correction of dehydration, electrolyte imbalance and hypotension by established procedures.

Lisinopril

Following a single oral dose of 20 mg/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*.)

Hydrochlorothiazide

Oral administration of a single oral dose of 10 mg/kg to mice and rats was not lethal. The most common signs and symptoms observed are those caused by electrolyte depletion (hypokalemia, hypochloremia, hyponatremia) and dehydration resulting from excessive diuresis. If digitalis has also been administered, hypokalemia may accentuate cardiac arrhythmias.

DOSAGE AND ADMINISTRATION

Lisinopril is an effective treatment of hypertension in once-daily doses of 10-80 mg, while hydrochlorothiazide is effective in doses of 12.5-50 mg. In clinical trials of lisinopril/hydrochlorothiazide combination therapy using lisinopril doses of 10-80 mg and hydrochlorothiazide doses of 6.25-50 mg, the antihypertensive response rates generally increased with increasing dose of either component.

The side effects (see WARNINGS) of lisinopril are generally rare and apparently independent of dose; those of hydrochlorothiazide are a mixture of dose-dependent phenomena (primarily hypokalemia) and dose-independent phenomena (e.g., pancreatitis), the former much more common than the latter. Therapy with any combination of lisinopril and hydrochlorothiazide will be associated with both sets of dose-independent side effects, but addition of lisinopril in clinical trials blunted the hypokalemia normally seen with diuretics.

To minimize dose-independent side effects, it is usually appropriate to begin combination therapy only after a patient has failed to achieve the desired effect with monotherapy.

Dose Titration Guided by Clinical Effect

A patient whose blood pressure is not adequately controlled with either lisinopril or hydrochlorothiazide monotherapy may be switched to PRINZIDE 10/12.5 or PRINZIDE 20/12.5. Further increases of either or both components could depend on clinical response. The hydrochlorothiazide dose should generally not be increased until 2-3 weeks have elapsed. Patients whose blood pressures are adequately controlled with 25 mg of daily hydrochlorothiazide, but who experience significant potassium loss with this regimen, may achieve similar or greater blood pressure control with less potassium loss if they are switched to PRINZIDE 10/12.5. Dosage higher than lisinopril 80 mg and hydrochlorothiazide 50 mg should not be used.

Replacement Therapy

The combination may be substituted for the titrated individual components.

Use in Renal Impairment

The usual regimens of therapy with PRINZIDE need not be adjusted as long as the patient's creatinine clearance is >30 mL/min/1.73 m^2 (serum creatinine approximately ≤3 mg/dL or 265 μmol/L). In patients with more severe renal impairment, loop diuretics are preferred to thiazides, so PRINZIDE is not recommended (see WARNINGS, *Anaphylactoid reactions during membrane exposure*).

HOW SUPPLIED

No. 8439 — Tablets PRINZIDE 10-12.5, are blue, hexagon-shaped tablets with code 145 on one side and plain on the other side. Each tablet contains 10 mg of lisinopril and 12.5 mg of hydrochlorothiazide. They are supplied as follows:

NDC 0006-0145-58 unit of use bottles of 100.

No. 8247 — Tablets PRINZIDE 20-12.5, are yellow, hexagon-shaped tablets with code MSD/140 on one side and scored on the other side. Each tablet contains 20 mg of lisinopril and 12.5 mg of hydrochlorothiazide. They are supplied as follows:

NDC 0006-0140-58 unit of use bottles of 100.

Storage

Store at controlled room temperature, 15-30°C (59-86°F). Protect from excessive light and humidity.

Dispense in a well-closed container, if product package is subdivided.

Manufactured for:
Merck Sharp & Dohme Corp., a subsidiary of
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by:
MERCK SHARP & DOHME LTD.
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