

ZESTORETIC[®]

(Lisinopril and Hydrochlorothiazide)

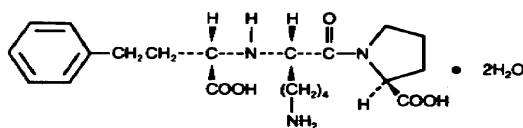
USE IN PREGNANCY

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, ZESTORETIC should be discontinued as soon as possible (See WARNINGS, Pregnancy, Lisinopril, Fetal/Neonatal Morbidity and Mortality).

DESCRIPTION

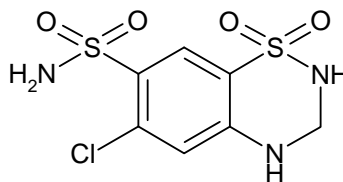
ZESTORETIC[®] (Lisinopril and Hydrochlorothiazide) combines an angiotensin converting enzyme inhibitor, lisinopril, and a diuretic, hydrochlorothiazide.

Lisinopril, a synthetic peptide derivative, is an oral long-acting angiotensin converting enzyme inhibitor. It is chemically described as (S)-1-[N2-(1-carboxy-3-phenylpropyl)-L-lysyl]-L-proline dihydrate. Its empirical formula is $C_{21}H_{31}N_3O_5 \cdot 2H_2O$ and its structural formula is:



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

Hydrochlorothiazide is 6-chloro-3,4-dihydro-2H-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 297.72, which is slightly soluble in water, but freely soluble in sodium hydroxide solution.

ZESTORETIC is available for oral use in three tablet combinations of lisinopril with hydrochlorothiazide: ZESTORETIC 10-12.5 containing 10 mg lisinopril and 12.5 mg hydrochlorothiazide; ZESTORETIC 20-12.5 containing 20 mg lisinopril and 12.5 mg hydrochlorothiazide; and, ZESTORETIC 20-25 containing 20 mg lisinopril and 25 mg hydrochlorothiazide.

Inactive Ingredients:

10-12.5 Tablets - calcium phosphate, magnesium stearate, mannitol, red ferric oxide, starch, yellow ferric oxide.

20-12.5 Tablets - calcium phosphate, magnesium stearate, mannitol, starch.

20-25 Tablets - calcium phosphate, magnesium stearate, mannitol, red ferric oxide, starch, yellow ferric oxide.

CLINICAL PHARMACOLOGY

Lisinopril and 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 ZESTORETIC 10-12.5 combination worked equally well in black and white patients. The ZESTORETIC 20-12.5 and ZESTORETIC 20-25 combinations appeared somewhat less effective in black patients, but relatively few black patients were studied. In most patients, the antihypertensive effect of ZESTORETIC was sustained for at least 24 hours.

In a randomized, controlled comparison, the mean antihypertensive effects of ZESTORETIC 20-12.5 and ZESTORETIC 20-25 were similar, suggesting that many patients who respond adequately to the latter combination may be controlled with ZESTORETIC 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 nonblack 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%) 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). In a multiple dose pharmacokinetic study in elderly versus young hypertensive patients using the lisinopril/hydrochlorothiazide combination, the AUC increased approximately 120% for lisinopril and approximately 80% for hydrochlorothiazide in older patients. 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 ¹⁴C 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

ZESTORETIC is indicated for the treatment of hypertension.

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

In using ZESTORETIC, 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 the use of ZESTORETIC, it should be noted that ACE inhibitors have been associated with a higher rate of angioedema in black than in nonblack patients (see WARNINGS, Lisinopril).

CONTRAINDICATIONS

ZESTORETIC 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. Because of the hydrochlorothiazide component, this product is contraindicated in patients with anuria or hypersensitivity to other sulfonamide-derived drugs.

WARNINGS

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 ZESTORETIC) 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 lisinopril. This may occur at any time during treatment. ACE inhibitors have been associated with a higher rate of angioedema in black than in nonblack patients. ZESTORETIC should be promptly discontinued and the 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).**

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.

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).

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:

Thiazide-containing combination products are not recommended in patients with severe renal dysfunction. Sudden and potentially life-threatening anaphylactoid reactions have been reported in some patients dialyzed with high-flux membranes (eg, AN69^{®*}) and treated concomitantly with an ACE inhibitor. In such patients, dialysis must be stopped immediately, and aggressive therapy for anaphylactoid reactions must 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 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).

Syncopal has been reported in 0.8 percent of patients receiving ZESTORETIC. 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 the 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.

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 lisinopril are insufficient to show that lisinopril 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.

Pregnancy

Lisinopril and Hydrochlorothiazide

Teratogenicity studies were conducted in mice and rats with up to 90 mg/kg/day of lisinopril (56 times the maximum recommended human dose) in combination with 10 mg/kg/day of hydrochlorothiazide (2.5 times the maximum recommended human dose). 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, ZESTORETIC 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 inhibitor therapy 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 ZESTORETIC 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, ZESTORETIC should be discontinued unless it is considered lifesaving for the mother. Contraction stress testing (CST), a nonstress 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 rats, mice, and rabbits. On a mg/kg basis, the doses used were up to 625 times (in mice), 188 times (in rats), and 0.6 times (in rabbits) the maximum recommended human dose.

Hydrochlorothiazide

Acute Myopia and Secondary Angle-Closure

Glaucoma: Hydrochlorothiazide, a sulfonamide, can cause an idiosyncratic reaction, resulting in acute transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of drug initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue hydrochlorothiazide as rapidly as possible. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulfonamide or penicillin allergy.

Teratogenic Effects: Reproduction studies in the rabbit, the mouse and the rat at doses up to 100 mg/kg/day (50 times the human dose) showed no evidence of external abnormalities of the fetus due to hydrochlorothiazide. Hydrochlorothiazide given in a two-litter study in rats at doses of 4-5.6 mg/kg/day (approximately 1-2 times the usual daily human dose) did not impair fertility or produce birth abnormalities in the offspring. Thiazides cross the placental barrier and appear in cord blood.

Nonteratogenic Effects: These may include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions have occurred in the adult.

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).

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. ZESTORETIC 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, almost 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 (eg, 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 ZESTORETIC. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to take no more drug until they have consulted with the prescribing physician.

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

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

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

Leukopenia/Neutropenia: Patients should be told to report promptly any indication of infection (eg, 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 ZESTORETIC 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: In some patients with compromised renal function who are being treated with non-steroidal anti-inflammatory drugs, the co-administration of lisinopril may result in a further deterioration of renal function. These effects are usually reversible. In a study in 36 patients with mild to moderate hypertension where the antihypertensive effects of lisinopril alone were compared to lisinopril given concomitantly with indomethacin, the use of indomethacin was associated with a reduced effect, although the difference between the two regimens was not significant.

Other Agents: 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 (eg, 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.

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 (eg, norepinephrine) - possible decreased response to pressor amines but not sufficient to preclude their use.

Skeletal muscle relaxants, nondepolarizing (eg, 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 ZESTORETIC.

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 ZESTORETIC and non-steroidal anti-inflammatory agents are used concomitantly, the patient should be observed closely to determine if the desired effect of ZESTORETIC is obtained.

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 ZESTORETIC.

Carcinogenesis, Mutagenesis, Impairment of Fertility Lisinopril and 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 and 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 for 105 weeks to male and female rats at doses up to 90 mg/kg/day (about 56 or 9 times* the maximum daily human dose, based on body weight and body surface area, respectively). There was no evidence of carcinogenicity when lisinopril was administered for 92 weeks to (male and female) mice at doses up to 135 mg/kg/day (about 84 times* the maximum recommended daily human dose). This dose was 6.8 times the maximum human dose based on body surface area in mice.

*Calculations assume a human weight of 50 kg and human body surface area of 1.62m².

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. This dose is 188 times and 30 times the maximum daily human dose based on mg/kg and mg/m², respectively.

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) or in male and female rats (at doses of up to approximately 100 mg/kg/day). These doses are 150 times and 12 times for mice and 25 times and 4 times for rats the maximum human daily dose based on mg/kg and mg/m², respectively. 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* nondisjunction 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 this dose is 25 times and 2 times the maximum daily human dose based on mg/kg and mg/m², respectively. In rats this dose is 1 times and 0.2 times the maximum daily human dose based on mg/kg and mg/m², respectively.

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 excreted in human milk. However, milk of lactating rats contains radioactivity following administration of ¹⁴C 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 adverse reactions in nursing infants from ACE inhibitors and hydrochlorothiazide, a decision should be made whether to discontinue nursing and/or discontinue ZESTORETIC, 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 ZESTORETIC 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.

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.

ADVERSE REACTIONS

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

In clinical trials with ZESTORETIC 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%), headache (5.2%), cough (3.9%), fatigue (3.7%) and orthostatic effects (3.2%) 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% 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 and 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% of patients in controlled trials and rarer, serious, possibly drug-related events reported in marketing experience are listed below:

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, cutaneous pseudolymphoma. **Special Senses:** Blurred vision, tinnitus, otalgia. **Urogenital:** Urinary tract infection.

Angioedema: Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported (See WARNINGS).

In rare cases, intestinal angioedema has been reported in post marketing experience.

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% 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 ZESTORETIC. 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% and 1.5 vol%, respectively) occurred frequently in hypertensive patients treated with ZESTORETIC but were rarely of clinical importance unless another cause of anemia coexisted. In clinical trials, 0.4% 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 ZESTORETIC. 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 ZESTORETIC: **Body as a Whole:** Anaphylactoid reactions (see WARNINGS, Anaphylactoid Reactions During Membrane Exposure), 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, inappropriate antidiuretic hormone secretion; **Hematologic:** Rare cases of bone marrow depression, hemolytic anemia, leukopenia/neutropenia, and thrombocytopenia have been reported in which a causal relationship to lisinopril can not 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 (eg, paresthesia, dysesthesia), spasm, hypersomnia, irritability; mood alterations (including depressive symptoms); **Respiratory:** Malignant lung neoplasms, hemoptysis, pulmonary edema, pulmonary infiltrates, bronchospasm, asthma, pleural effusion, pneumonia, eosinophilic pneumonitis, 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, rare cases of other severe skin reactions, including toxic epidermal necrolysis and Stevens-Johnson Syndrome (causal relationship has not been established); **Special Senses:** Visual loss, diplopia, photophobia, taste alteration, olfactory disturbance; **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, eosinophilia and leukocytosis. Rash, photosensitivity or other dermatological manifestations may occur alone or in combination with these symptoms.

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) (See WARNINGS, Hepatic Failure), pancreatitis, sialoadenitis, 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 angitis (vasculitis and cutaneous vasculitis), respiratory distress including pneumonitis and pulmonary edema, anaphylactic reactions.

OVERDOSAGE

No specific information is available on the treatment of overdose with ZESTORETIC. Treatment is symptomatic and supportive. Therapy with ZESTORETIC 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 g/kg no lethality occurred in rats and death occurred in one of 20 mice receiving the same dose. The most likely manifestation of overdose 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 Reaction During Membrane Exposure).

Hydrochlorothiazide

Oral administration of a single oral dose of 10 g/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 monotherapy is an effective treatment of hypertension in once-daily doses of 10-80 mg, while hydrochlorothiazide monotherapy is effective in doses of 12.5 - 50 mg per day. 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 (eg, pancreatitis), the former much more common than the latter. Therapy with any combination of lisinopril and hydrochlorothiazide may be associated with either or both dose-independent or dose-dependent side effects, but addition of lisinopril in clinical trials blunted the hypokalemia normally seen with diuretics.

To minimize dose-dependent 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 lisinopril/HCTZ 10/12.5 or lisinopril/HCTZ 20/12.5, depending on current monotherapy dose. Further increases of either or both components should depend on clinical response with blood pressure measured at the interdosing interval to ensure that there is an adequate antihypertensive effect at that time. The hydrochlorothiazide dose should generally not be increased until 2-3 weeks have elapsed. After addition of the diuretic it may be possible to reduce the dose of lisinopril. 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 without electrolyte disturbance if they are switched to lisinopril/HCTZ 10/12.5.

In patients who are currently being treated with a diuretic, symptomatic hypotension occasionally may occur following the initial dose of lisinopril. The diuretic should, if possible, be discontinued for two to three days before beginning therapy with lisinopril to reduce the likelihood of hypotension (See WARNINGS). If the patient's blood pressure is not controlled with lisinopril alone, diuretic therapy may be resumed.

If the diuretic cannot be discontinued, an initial dose of 5 mg of lisinopril 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 ZESTORETIC with potassium supplements, potassium salt substitutes or potassium-sparing diuretics may lead to increases of serum potassium (See PRECAUTIONS).

Replacement Therapy: The combination may be substituted for the titrated individual components.

Use in Renal Impairment: Regimens of therapy with lisinopril/HCTZ need not take account of renal function as long as the patient's creatinine clearance is >30 mL/min/1.7m² (serum creatinine roughly ≤ 3 mg/dL or 265 μ mol/L). In patients with more severe renal impairment, loop diuretics are preferred to thiazides, so lisinopril/HCTZ is not recommended (see WARNINGS, Anaphylactoid Reactions During Membrane Exposure).

HOW SUPPLIED

ZESTORETIC 10-12.5 Tablets (NDC 0310-0141) Peach, round, biconvex, uncoated tablets identified with "141" debossed on one side and "ZESTORETIC" on the other side are supplied in bottles of 100 tablets.

ZESTORETIC 20-12.5 Tablets (NDC 0310-0142) White, round, biconvex, uncoated tablets identified with "142" debossed on one side and "ZESTORETIC" on the other side are supplied in bottles of 100 tablets.

ZESTORETIC 20-25 Tablets (NDC 0310-0145) Peach, round, biconvex, uncoated tablets identified with "145" debossed on one side and "ZESTORETIC" on the other side are supplied in bottles of 100 tablets.

Storage

Store at controlled room temperature, 20-25°C (68-77°F) [see USP]. Protect from excessive light and humidity.

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Wilmington, DE 19850

SIC xxxxx-xx

Rev. 02/11

AstraZeneca

ATACAND HCT[®]
(candesartan cilexetil –
hydrochlorothiazide)
TABLETS

USE IN PREGNANCY

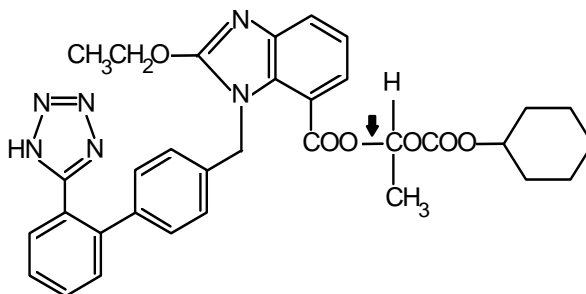
When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. When pregnancy is detected, ATACAND HCT should be discontinued as soon as possible. See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

DESCRIPTION

ATACAND HCT (candesartan cilexetil-hydrochlorothiazide) combines an angiotensin II receptor (type AT₁) antagonist and a diuretic, hydrochlorothiazide.

Candesartan cilexetil, a nonpeptide, is chemically described as (±)-1-Hydroxyethyl 2-ethoxy-1-[p-(o-1H-tetrazol-5-ylphenyl)benzyl]-7-benzimidazolecarboxylate, cyclohexyl carbonate (ester).

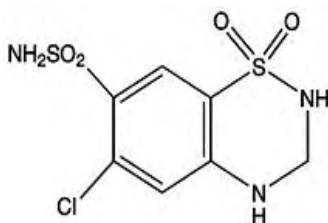
Its empirical formula is C₃₃H₃₄N₆O₆, and its structural formula is



↓ site of ester hydrolysis.

Candesartan cilexetil is a white to off-white powder with a molecular weight of 610.67. It is practically insoluble in water and sparingly soluble in methanol. Candesartan cilexetil is a racemic mixture containing one chiral center at the cyclohexyloxycarbonyloxy ethyl ester group. Following oral administration, candesartan cilexetil undergoes hydrolysis at the ester link to form the active drug, candesartan, which is achiral.

Hydrochlorothiazide is 6-chloro-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide. Its empirical formula is C₇H₈ClN₃O₄S₂ and its structural formula is



Hydrochlorothiazide is a white, or practically white, crystalline powder with a molecular weight of 297.72, which is slightly soluble in water, but freely soluble in sodium hydroxide solution.

ATACAND HCT is available for oral administration in three tablet strengths of candesartan cilexetil and hydrochlorothiazide.

ATACAND HCT 16-12.5 contains 16 mg of candesartan cilexetil and 12.5 mg of hydrochlorothiazide. ATACAND HCT 32-12.5 contains 32 mg of candesartan cilexetil and 12.5 mg of hydrochlorothiazide. ATACAND HCT 32-25 contains 32 mg of candesartan cilexetil and 25 mg of hydrochlorothiazide. The inactive ingredients of the tablets are carboxymethylcellulose calcium, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate, corn starch, polyethylene glycol 8000, and ferric oxide (yellow). Ferric oxide (reddish brown) is also added to the 16-12.5 mg and 32-25 mg tablets as colorant.

CLINICAL PHARMACOLOGY

Mechanism of Action

Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin-converting enzyme (ACE, kininase

II). Angiotensin II is the principal pressor agent of the renin-angiotensin system, with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation, and renal reabsorption of sodium. Candesartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT₁ receptor in many tissues, such as vascular smooth muscle and the adrenal gland. Its action is, therefore, independent of the pathways for angiotensin II synthesis.

There is also an AT₂ receptor found in many tissues, but AT₂ is not known to be associated with cardiovascular homeostasis. Candesartan has much greater affinity (>10,000-fold) for the AT₁ receptor than for the AT₂ receptor.

Blockade of the renin-angiotensin system with ACE inhibitors, which inhibit the biosynthesis of angiotensin II from angiotensin I, is widely used in the treatment of hypertension. ACE inhibitors also inhibit the degradation of bradykinin, a reaction also catalyzed by ACE. Because candesartan does not inhibit ACE (kininase II), it does not affect the response to bradykinin. Whether this difference has clinical relevance is not yet known. Candesartan does not bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

Blockade of the angiotensin II receptor inhibits the negative regulatory feedback of angiotensin II on renin secretion, but the resulting increased plasma renin activity and angiotensin II circulating levels do not overcome the effect of candesartan on blood pressure.

Hydrochlorothiazide is a thiazide diuretic. Thiazides affect the renal tubular mechanisms of electrolyte reabsorption, directly increasing excretion of sodium and chloride in approximately equivalent amounts. Indirectly, the diuretic action of hydrochlorothiazide reduces plasma volume, with consequent increases in plasma renin activity, increases in aldosterone secretion, increases in urinary potassium loss, and decreases in serum potassium. The renin-aldosterone link is mediated by angiotensin II, so coadministration of an angiotensin II receptor antagonist tends to reverse the potassium loss associated with these diuretics.

The mechanism of the antihypertensive effect of thiazides is unknown.

Pharmacokinetics

General

Candesartan Cilexetil

Candesartan cilexetil is rapidly and completely bioactivated by ester hydrolysis during absorption from the gastrointestinal tract to candesartan, a selective AT₁ subtype angiotensin II receptor antagonist. Candesartan is mainly excreted unchanged in urine and feces (via bile). It undergoes minor hepatic metabolism by O-deethylation to an inactive metabolite. The elimination half-life of candesartan is approximately 9 hours. After single and repeated administration, the pharmacokinetics of candesartan are linear for oral doses up to 32 mg of candesartan cilexetil. Candesartan and its inactive metabolite do not accumulate in serum upon repeated once-daily dosing.

Following administration of candesartan cilexetil, the absolute bioavailability of candesartan was estimated to be 15%. After tablet ingestion, the peak serum concentration (C_{max}) is reached after 3 to 4 hours. Food with a high fat content does not affect the bioavailability of candesartan after candesartan cilexetil administration.

Hydrochlorothiazide

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.

Metabolism and Excretion

Candesartan Cilexetil

Total plasma clearance of candesartan is 0.37 mL/min/kg, with a renal clearance of 0.19 mL/min/kg. When candesartan is administered orally, about 26% of the dose is excreted unchanged in urine. Following an oral dose of ¹⁴C-labeled candesartan cilexetil, approximately 33% of radioactivity is recovered in urine and approximately 67% in feces. Following an intravenous dose of ¹⁴C-labeled candesartan, approximately 59% of radioactivity is recovered in urine and approximately 36% in feces. Biliary excretion contributes to the elimination of candesartan.

Hydrochlorothiazide:

Hydrochlorothiazide is not metabolized but is eliminated rapidly by the kidney. At least 61% of the oral dose is eliminated unchanged within 24 hours.

Distribution

Candesartan Cilexetil

The volume of distribution of candesartan is 0.13 L/kg. Candesartan is highly bound to plasma proteins (>99%) and does not penetrate red blood cells. The protein binding is constant at candesartan plasma concentrations well above the range achieved with recommended doses. In rats, it has been demonstrated that candesartan crosses the blood-brain barrier poorly, if at all. It has also been demonstrated in rats that candesartan passes across the placental barrier and is distributed in the fetus.

Hydrochlorothiazide

Hydrochlorothiazide crosses the placental but not the blood-brain barrier and is excreted in breast milk.

Special Populations

Pediatric

The pharmacokinetics of candesartan cilexetil have not been investigated in patients <18 years of age.

Geriatric

The pharmacokinetics of candesartan have been studied in the elderly (≥ 65 years). The plasma concentration of candesartan was higher in the elderly (C_{\max} was approximately 50% higher, and AUC was approximately 80% higher) compared to younger subjects administered the same dose. The pharmacokinetics of candesartan were linear in the elderly, and candesartan and its inactive metabolite did not accumulate in the serum of these subjects upon repeated, once-daily administration. No initial dosage adjustment is necessary. (See DOSAGE AND ADMINISTRATION.)

Gender

There is no difference in the pharmacokinetics of candesartan between male and female subjects.

Renal Insufficiency

In hypertensive patients with renal insufficiency, serum concentrations of candesartan were elevated. After repeated dosing, the AUC and C_{max} were approximately doubled in patients with severe renal impairment (creatinine clearance <30 mL/min/1.73m²) compared to patients with normal kidney function. The pharmacokinetics of candesartan in hypertensive patients undergoing hemodialysis are similar to those in hypertensive patients with severe renal impairment. Candesartan cannot be removed by hemodialysis. No initial dosage adjustment is necessary in patients with renal insufficiency.

Thiazide diuretics are eliminated by the kidney, with a terminal half-life of 5-15 hours. In a study of patients with impaired renal function (mean creatinine clearance of 19 mL/min), the half-life of hydrochlorothiazide elimination was lengthened to 21 hours. (See DOSAGE AND ADMINISTRATION.)

Hepatic Insufficiency

The pharmacokinetics of candesartan were compared in patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment to matched healthy volunteers following a single dose of 16 mg candesartan cilexetil. The AUC for candesartan in patients with mild and moderate hepatic impairment was increased 30% and 145% respectively. The C_{max} for candesartan was increased 56% and 73% respectively. The pharmacokinetics of candesartan in severe hepatic impairment have not been studied. No dose adjustment is recommended for patients with mild hepatic impairment. In patients with moderate hepatic impairment, consideration should be given to initiation of ATACAND at a lower dose, such as 8 mg. If a lower starting dose is selected for candesartan cilexetil, ATACAND HCT is not recommended for initial titration because the appropriate initial starting dose of candesartan cilexetil cannot be given. (See DOSAGE AND ADMINISTRATION).

Thiazide diuretics should be used with caution in patients with hepatic impairment. (See DOSAGE AND ADMINISTRATION.)

Pharmacodynamics

Candesartan Cilexetil

Candesartan inhibits the pressor effects of angiotensin II infusion in a dose-dependent manner. After 1 week of once-daily dosing with 8 mg of candesartan cilexetil, the pressor effect was inhibited by approximately 90% at peak with approximately 50% inhibition persisting for 24 hours.

Plasma concentrations of angiotensin I and angiotensin II, and plasma renin activity (PRA), increased in a dose-dependent manner after single and repeated administration of candesartan cilexetil to healthy subjects and hypertensive patients. ACE activity was not altered in healthy subjects after repeated candesartan cilexetil administration. The once-daily administration of up to 16 mg of candesartan cilexetil to healthy subjects did not influence plasma aldosterone concentrations, but a decrease in the plasma concentration of aldosterone was observed when 32 mg of candesartan cilexetil was administered to hypertensive patients. In spite of the effect of candesartan cilexetil on aldosterone secretion, very little effect on serum potassium was observed.

In multiple-dose studies with hypertensive patients, there were no clinically significant changes in metabolic function including serum levels of total cholesterol, triglycerides, glucose, or uric acid. In a 12-week study of 161 patients with non-insulin-dependent (type 2) diabetes mellitus and hypertension, there was no change in the level of HbA_{1c}.

Hydrochlorothiazide

After oral administration of hydrochlorothiazide, diuresis begins within 2 hours, peaks in about 4 hours and lasts about 6 to 12 hours.

Clinical Trials

Candesartan Cilexetil–Hydrochlorothiazide

Of 12 controlled clinical trials involving 4588 patients, 5 were double-blind, placebo controlled and evaluated the antihypertensive effects of single entities vs the combination. These 5 trials, of 8 to 12 weeks duration, randomized 3037 hypertensive patients. Doses ranged from 2 to 32 mg candesartan cilexetil and from 6.25 to 25 mg hydrochlorothiazide administered once daily in various combinations.

The combination of candesartan cilexetil-hydrochlorothiazide resulted in placebo-adjusted decreases in sitting systolic and diastolic blood pressures of 14-18/8-11 mm Hg at doses of 16-12.5 mg and 32-12.5 mg. The combination of candesartan cilexetil and hydrochlorothiazide 32-25 mg resulted in placebo-adjusted decreases in sitting systolic and diastolic blood pressures of 16-19/9-11 mm Hg. The placebo corrected trough to peak ratio was evaluated in a study of candesartan cilexetil-hydrochlorothiazide 32-12.5 mg and was 88%.

Most of the antihypertensive effect of the combination of candesartan cilexetil and hydrochlorothiazide was seen in 1 to 2 weeks with the full effect observed within 4 weeks. In long-term studies of up to 1 year, the blood pressure lowering effect of the combination was maintained. The antihypertensive effect was similar regardless of age or gender, and overall response to the combination was similar in black and non-black patients. No appreciable changes in heart rate were observed with combination therapy in controlled trials.

INDICATIONS AND USAGE

ATACAND HCT is indicated for the treatment of hypertension. This fixed dose combination is not indicated for initial therapy (see DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

ATACAND HCT is contraindicated in patients who are hypersensitive to any component of this product.

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

WARNINGS

Fetal/Neonatal Morbidity and Mortality

Drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature in patients who were taking angiotensin-converting enzyme inhibitors. Post-marketing experience has identified reports of fetal and neonatal toxicity in babies born to women treated with candesartan cilexetil during pregnancy. Because candesartan cilexetil is a component of ATACAND HCT, when pregnancy is detected, ATACAND HCT should be discontinued as soon as possible.

The use of drugs that act directly on the renin-angiotensin system 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 exposure to the drug.

These adverse effects do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to an angiotensin II receptor antagonist only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should have the patient discontinue the use of ATACAND HCT as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to a drug acting on the renin-angiotensin system 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 intra-amniotic environment.

If oligohydramnios is observed, ATACAND HCT should be discontinued unless it is considered life saving for the mother. Contraction stress testing (CST), a nonstress 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 an angiotensin II receptor antagonist 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.

Candesartan Cilexetil-Hydrochlorothiazide

There was no evidence of teratogenicity or other adverse effects on embryo-fetal development when pregnant mice, rats or rabbits were treated orally with candesartan cilexetil alone or in combination with hydrochlorothiazide. For mice, the maximum dose of candesartan cilexetil was 1000 mg/kg/day (about 150 times the maximum recommended daily human dose [MRHD]*). For rats, the maximum dose of candesartan cilexetil was 100 mg/kg/day (about 31 times the MRHD*). For rabbits, the maximum dose of candesartan cilexetil was 1 mg/kg/day (a maternally toxic dose that is about half the MRHD*). In each of these studies, hydrochlorothiazide was tested at the same dose level (10 mg/kg/day, about 4, 8, and 15 times the MRHD* in mouse, rats, and rabbit, respectively). There was no evidence of harm to the rat or mouse fetus or embryo in studies in which hydrochlorothiazide was administered alone to the pregnant rat or mouse at doses of up to 1000 and 3000 mg/kg/day, respectively.

* Doses compared on the basis of body surface area. MRHD considered to be 32 mg for candesartan cilexetil and 12.5 mg for hydrochlorothiazide.

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.

Hypotension in Volume- and Salt-Depleted Patients

Based on adverse events reported from all clinical trials of ATACAND HCT, excessive reduction of blood pressure was rarely seen in patients with uncomplicated hypertension treated with candesartan cilexetil and hydrochlorothiazide (0.4%). Initiation of antihypertensive therapy may cause symptomatic hypotension in patients with intravascular volume- or sodium- depletion, eg, in patients treated vigorously with diuretics or in patients on dialysis. These conditions should be corrected prior to administration of ATACAND HCT, or the treatment should start under close medical supervision (see DOSAGE AND ADMINISTRATION).

If hypotension occurs, the patients should be placed in the supine position and, if necessary, given an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further treatment which usually can be continued without difficulty once the blood pressure has stabilized.

Hydrochlorothiazide

Acute Myopia and Secondary Angle-Closure Glaucoma: Hydrochlorothiazide, a sulfonamide, can cause an idiosyncratic reaction, resulting in acute transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of drug initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue hydrochlorothiazide as rapidly as possible. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulfonamide or penicillin allergy.

Impaired Hepatic Function

Thiazide diuretics 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.

Hypersensitivity Reaction

Hypersensitivity reactions to hydrochlorothiazide may occur in patients with or without a history of allergy or bronchial asthma, but are more likely in patients with such a history.

Systemic Lupus Erythematosus

Thiazide diuretics have been reported to cause exacerbation or activation of systemic lupus erythematosus.

Lithium Interaction

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

PRECAUTIONS

General

Candesartan Cilexetil–Hydrochlorothiazide

In clinical trials of various doses of candesartan cilexetil and hydrochlorothiazide, the incidence of hypertensive patients who developed hypokalemia (serum potassium <3.5 mEq/L) was 2.5% versus 2.1% for placebo; the incidence of hyperkalemia (serum potassium >5.7 mEq/L) was 0.4% versus 1.0% for placebo. No patient receiving ATACAND HCT 16-12.5 mg or 32-12.5 mg was discontinued due to increases or decreases in serum potassium. Overall, the combination of candesartan cilexetil and hydrochlorothiazide had no clinically significant effect on serum potassium.

Candesartan

Major Surgery/Anesthesia— Hypotension may occur during major surgery and anesthesia in patients treated with angiotensin II receptor antagonists, including candesartan, due to blockade of the renin-angiotensin system. Very rarely, hypotension may be severe such that it may warrant the use of intravenous fluids and/or vasopressors.

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 (eg, increased ventricular irritability).

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 acute 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 post-sympathectomy 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.

Impaired Renal Function

Candesartan Cilexetil

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals treated with candesartan cilexetil. In patients whose renal function may depend upon the activity of the renin-angiotensin-aldosterone system (eg, patients with severe congestive heart failure), treatment with angiotensin-converting enzyme inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. Similar results may be anticipated in patients treated with candesartan cilexetil. (See CLINICAL PHARMACOLOGY, Special Populations.)

In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen (BUN) have been reported. There has been no long-term use of candesartan cilexetil in patients with unilateral or bilateral renal artery stenosis, but similar results may be expected.

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.

Impaired Hepatic Function

Candesartan Cilexetil

Based on pharmacokinetic data significant increases in candesartan AUC and C_{max} in patients with moderate hepatic impairment have been demonstrated. (See CLINICAL PHARMACOLOGY, Special Populations.)

Information for Patients

Pregnancy

Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to drugs that act on the renin-angiotensin system, and they should also be told that these consequences do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

Symptomatic Hypotension

A patient receiving ATACAND HCT should be cautioned that lightheadedness can occur, especially during the first days of therapy, and that it should be reported to the prescribing physician. The patients should be told that if syncope occurs, ATACAND HCT should be discontinued until the physician has been consulted.

All patients should be cautioned that inadequate fluid intake, excessive perspiration, diarrhea, or vomiting can lead to an excessive fall in blood pressure, with the same consequences of lightheadedness and possible syncope.

Potassium Supplements

A patient receiving ATACAND HCT should be told not to use potassium supplements or salt substitutes containing potassium without consulting the prescribing physician.

Drug Interactions

Candesartan Cilexetil

No significant drug interactions have been reported in studies of candesartan cilexetil given with other drugs such as glyburide, nifedipine, digoxin, warfarin, hydrochlorothiazide, and oral contraceptives in healthy volunteers. Because candesartan is not significantly metabolized by the cytochrome P450 system and at therapeutic concentrations has no effects on P450 enzymes, interactions with drugs that inhibit or are metabolized by those enzymes would not be expected.

Lithium

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors, and with some angiotensin II receptor antagonists. An increase in serum lithium concentration has been reported during concomitant administration of lithium with candesartan cilexetil, so careful monitoring of serum lithium levels is recommended during concomitant use.

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 (eg, norepinephrine) – Possible decreased response to pressor amines but not sufficient to preclude their use.

Skeletal muscle relaxants, nondepolarizing (eg, tubocurarine)
– Possible increased responsiveness to the muscle relaxant.

Lithium – Generally should not 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 ATACAND HCT.

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 ATACAND HCT and non-steroidal anti-inflammatory agents are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity studies have been conducted with the combination of candesartan cilexetil and hydrochlorothiazide. There was no evidence of carcinogenicity when candesartan cilexetil was orally administered to mice and rats for up to 104 weeks at doses up to 100 and 1000 mg/kg/day, respectively. Rats received the drug by gavage whereas mice received the drug by dietary administration. These (maximally-tolerated) doses of candesartan cilexetil provided systemic exposures to candesartan (AUCs) that were, in mice, approximately 7 times and, in rats, more than 70 times the exposure in man at the maximum recommended daily human dose (32 mg). 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) or in male and female rats (at doses of up to approximately 100 mg/kg/day). The NTP, however, found equivocal evidence for hepatocarcinogenicity in male mice.

Candesartan cilexetil or candesartan (the active metabolite), in combination with hydrochlorothiazide, tested positive *in vitro* in the Chinese hamster lung (CHL) chromosomal aberration assay and mouse lymphoma mutagenicity assay. The candesartan cilexetil/hydrochlorothiazide combination tested negative for mutagenicity in bacteria (Ames test), for unscheduled DNA synthesis in rat liver, for chromosomal aberrations in rat bone marrow and for micronuclei in mouse bone marrow.

Both candesartan and its O-deethyl metabolite tested positive for genotoxicity in the *in vitro* CHL chromosomal aberration assay. Neither compound tested positive in the Ames microbial mutagenesis assay or in the *in vitro* mouse lymphoma cell assay. Candesartan (but not its O-deethyl metabolite) was also evaluated *in vivo* in the mouse micronucleus test and *in vitro* in the Chinese hamster ovary (CHO) gene mutation assay, in both cases with negative results. Candesartan cilexetil was evaluated in the Ames test, the *in vitro* mouse lymphoma cell assay, the *in vivo* rat hepatocyte unscheduled DNA synthesis assay and the *in vivo* mouse micronucleus test, in each case with negative results. Candesartan cilexetil was not evaluated in the CHL chromosomal aberration or CHO gene mutation assays.

When hydrochlorothiazide was tested alone, positive results were obtained *in vitro* in the CHO sister chromatid exchange (clastogenicity) and mouse lymphoma cell (mutagenicity) assays and in the *Aspergillus nidulans* non-disjunction assay. Hydrochlorothiazide was not genotoxic *in vitro* in the Ames test for point mutations and the 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.

No fertility studies have been conducted with the combination of candesartan cilexetil and hydrochlorothiazide. Fertility and reproductive performance were not affected in studies with male and female rats given oral doses of up to 300 mg candesartan cilexetil/kg/day (83 times the maximum daily human dose of 32 mg on a body surface area basis). 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.

Pregnancy

Pregnancy Categories C (first trimester) and D (second and third trimesters)

See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

Nursing Mothers

It is not known whether candesartan is excreted in human milk, but candesartan has been shown to be present in rat milk. Thiazides appear in human milk. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, 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

Of the total number of subjects in all clinical studies of ATACAND HCT (2831), 611 (22%) were 65 and over, while 94 (3%) were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Hydrochlorothiazide 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.

ADVERSE REACTIONS

Candesartan Cilexetil-Hydrochlorothiazide

ATACAND HCT has been evaluated for safety in more than 2800 patients treated for hypertension. More than 750 of these patients were studied for at least six months and more than 500 patients were treated for at least one year. Adverse experiences have generally been mild and transient in nature and have only infrequently required discontinuation of therapy. The overall incidence of adverse events reported with ATACAND HCT was comparable to placebo. The overall frequency of adverse experiences was not related to dose, age, gender, or race.

In placebo-controlled trials that included 1089 patients treated with various combinations of candesartan cilexetil (doses of 2-32 mg) and hydrochlorothiazide (doses of 6.25-25 mg) and 592 patients treated with placebo, adverse events, whether or not attributed to treatment, occurring in greater than 2% of patients treated with ATACAND HCT and that were more frequent for ATACAND HCT than placebo were: **Respiratory System Disorder:** upper respiratory tract infection (3.6% vs 3.0%); **Body as a Whole:** back pain (3.3% vs 2.4%); influenza-like symptoms (2.5% vs 1.9%); **Central/Peripheral Nervous System:** dizziness (2.9% vs 1.2%).

The frequency of headache was greater than 2% (2.9%) in patients treated with ATACAND HCT but was less frequent than the rate in patients treated with placebo (5.2%).

Other adverse events that have been reported, whether or not attributed to treatment, with an incidence of 0.5% or greater from the more than 2800 patients worldwide treated with ATACAND HCT included: ***Body as a Whole:*** inflicted injury, fatigue, pain, chest pain, peripheral edema, asthenia; ***Central and Peripheral Nervous System:*** vertigo, paresthesia, hypesthesia; ***Respiratory System Disorders:*** bronchitis, sinusitis, pharyngitis, coughing, rhinitis, dyspnea; ***Musculoskeletal System Disorders:*** arthralgia, myalgia, arthrosis, arthritis, leg cramps, sciatica; ***Gastrointestinal System Disorders:*** nausea, abdominal pain, diarrhea, dyspepsia, gastritis, gastroenteritis, vomiting; ***Metabolic and Nutritional Disorders:*** hyperuricemia, hyperglycemia, hypokalemia, increased BUN, creatine phosphokinase increased; ***Urinary System Disorders:*** urinary tract infection, hematuria, cystitis; ***Liver/Biliary System Disorders:*** hepatic function abnormal, increased transaminase levels; ***Heart Rate and Rhythm Disorders:*** tachycardia, palpitation, extrasystoles, bradycardia; ***Psychiatric Disorders:*** depression, insomnia, anxiety; ***Cardiovascular Disorders:*** ECG abnormal; ***Skin and Appendages Disorders:*** eczema, sweating increased, pruritus, dermatitis, rash; ***Platelet/Bleeding-Clotting Disorders:*** epistaxis; ***Resistance Mechanism Disorders:*** infection, viral infection; ***Vision Disorders:*** conjunctivitis; ***Hearing and Vestibular Disorders:*** tinnitus.

Reported events seen less frequently than 0.5% included angina pectoris, myocardial infarction and angioedema.

Candesartan Cilexetil

Other adverse experiences that have been reported with candesartan cilexetil, without regard to causality, were: ***Body as a Whole:*** fever; ***Metabolic and Nutritional Disorders:*** hypertriglyceridemia; ***Psychiatric Disorders:*** somnolence; ***Urinary System Disorders:*** albuminuria.

Post-Marketing Experience

The following have been very rarely reported in post-marketing experience with candesartan cilexetil:

Digestive: Abnormal hepatic function and hepatitis.

Hematologic: Neutropenia, leukopenia, and agranulocytosis.

Metabolic and Nutritional Disorders: hyperkalemia, hyponatremia.

Renal: renal impairment, renal failure.

Skin and Appendages Disorders: Pruritus and urticaria.

Rare reports of rhabdomyolysis have been reported in patients receiving angiotensin II receptor blockers.

Hydrochlorothiazide

Other adverse experiences that have been reported with hydrochlorothiazide, without regard to causality, are listed below:

Body As A Whole: weakness; **Cardiovascular:** hypotension including orthostatic hypotension (may be aggravated by alcohol, barbiturates, narcotics or antihypertensive drugs); **Digestive:** pancreatitis, jaundice (intrahepatic cholestatic jaundice), sialadenitis, cramping, constipation, gastric irritation, anorexia; **Hematologic:** aplastic anemia, agranulocytosis, leukopenia, hemolytic anemia, thrombocytopenia; **Hypersensitivity:** anaphylactic reactions, necrotizing angiitis (vasculitis and cutaneous vasculitis), respiratory distress including pneumonitis and pulmonary edema, photosensitivity, urticaria, purpura; **Metabolic:** electrolyte imbalance, glycosuria; **Musculoskeletal:** muscle spasm; **Nervous System/Psychiatric:** restlessness; **Renal:** renal failure, renal dysfunction, interstitial nephritis; **Skin:** erythema multiforme including Stevens-Johnson syndrome, exfoliative dermatitis including toxic epidermal necrolysis, alopecia; **Special Senses:** transient blurred vision, xanthopsia; **Urogenital:** impotence.

Laboratory Test Findings

In controlled clinical trials, clinically important changes in standard laboratory parameters were rarely associated with the administration of ATACAND HCT.

Creatinine, Blood Urea Nitrogen — Minor increases in blood urea nitrogen (BUN) and serum creatinine were observed infrequently. One patient was discontinued from ATACAND HCT due to increased BUN. No patient was discontinued due to an increase in serum creatinine.

Hemoglobin and Hematocrit — Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.2 g/dL and 0.4 volume percent, respectively) were observed in patients treated with ATACAND HCT, but were rarely of clinical importance.

Potassium — A small decrease (mean decrease of 0.1 mEq/L) was observed in patients treated with ATACAND HCT. In placebo-controlled trials, hypokalemia was reported in 0.4% of patients treated with ATACAND HCT as compared to 1.0% of patients treated with hydrochlorothiazide or 0.2% of patients treated with placebo.

Liver Function Tests — Occasional elevations of liver enzymes and/or serum bilirubin have occurred.

OVERDOSAGE

Candesartan Cilexetil – Hydrochlorothiazide

No lethality was observed in acute toxicity studies in mice, rats and dogs given single oral doses of up to 2000 mg/kg of candesartan cilexetil or in rats given single oral doses of up to 2000 mg/kg of candesartan cilexetil in combination with 1000 mg/kg of hydrochlorothiazide. In mice given single oral doses of the primary metabolite, candesartan, the minimum lethal dose was greater than 1000 mg/kg but less than 2000 mg/kg.

Limited data are available in regard to overdosage with candesartan cilexetil in humans. The most likely manifestations of overdosage with candesartan cilexetil would be hypotension, dizziness, and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension should occur, supportive treatment should be initiated. For hydrochlorothiazide, 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.

Candesartan cannot be removed by hemodialysis. The degree to which hydrochlorothiazide is removed by hemodialysis has not been established.

Treatment

To obtain up-to-date information about the treatment of overdose, consult your Regional Poison Control Center. Telephone numbers of certified poison control centers are listed in the *Physicians' Desk Reference (PDR)*. In managing overdose, consider the possibilities of multiple-drug overdoses, drug-drug interactions, and altered pharmacokinetics in your patient.

DOSAGE AND ADMINISTRATION

The usual recommended starting dose of candesartan cilexetil is 16 mg once daily when it is used as monotherapy in patients who are not volume depleted. ATACAND can be administered once or twice daily with total daily doses ranging from 8 mg to 32 mg. Patients requiring further reduction in blood pressure should be titrated to 32 mg. Doses larger than 32 mg do not appear to have a greater blood pressure lowering effect.

Hydrochlorothiazide is effective in doses of 12.5 to 50 mg once daily.

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.

The side effects (See WARNINGS) of candesartan cilexetil are generally rare and apparently independent of dose; those of hydrochlorothiazide are a mixture of dose-dependent phenomena (primarily hypokalemia) and dose-independent phenomena (eg, pancreatitis), the former much more common than the latter.

Therapy with any combination of candesartan cilexetil and hydrochlorothiazide will be associated with both sets of dose-independent side effects.

Replacement Therapy: The combination may be substituted for the titrated components.

Dose Titration by Clinical Effect: A patient whose blood pressure is not controlled on 25 mg of hydrochlorothiazide once daily can expect an incremental effect from ATACAND HCT 16-12.5 mg. A patient whose blood pressure is controlled on 25 mg of hydrochlorothiazide but is experiencing decreases in serum potassium can expect the same or incremental blood pressure effects from ATACAND HCT 16-12.5 mg and serum potassium may improve.

A patient whose blood pressure is not controlled on 32 mg of ATACAND can expect incremental blood pressure effects from ATACAND HCT 32-12.5 mg and then 32-25 mg. The maximal antihypertensive effect of any dose of ATACAND HCT can be expected within 4 weeks of initiating that dose.

Patients with Renal Impairment: The usual regimens of therapy with ATACAND HCT may be followed as long as the patient's creatinine clearance is > 30 mL/min. In patients with more severe renal impairment, loop diuretics are preferred to thiazides, so ATACAND HCT is not recommended.

Patients with Hepatic Impairment: The usual regimens of therapy with ATACAND HCT may be followed in patients with mild hepatic impairment. In patients with moderate hepatic impairment, consideration should be given to initiation of ATACAND at a lower dose, such as 8 mg. If a lower starting dose is selected for candesartan cilexetil, ATACAND HCT is not recommended for initial titration because the appropriate initial starting dose of candesartan cilexetil cannot be given. (See CLINICAL PHARMACOLOGY, Special Populations, *Hepatic Insufficiency*).

Thiazide diuretics should be used with caution in patients with hepatic impairment; therefore, care should be exercised with dosing of ATACAND HCT.

ATACAND HCT may be administered with other antihypertensive agents.

ATACAND HCT may be administered with or without food.

HOW SUPPLIED

No. 3825 — Tablets ATACAND HCT 16-12.5 mg, are peach, oval, biconvex, non-film-coated tablets, scored on both sides and coded with ACS on one side. They are supplied as follows:

NDC 0186-0162-28 unit dose packages of 100.

NDC 0186-0162-54 unit of use bottles of 90.

No. 3826 — Tablets ATACAND HCT 32-12.5 mg, are yellow, oval, biconvex, non-film-coated tablets, scored on both sides and coded with ACJ on one side. They are supplied as follows:

NDC 0186-0322-28 unit dose packages of 100.

NDC 0186-0322-54 unit of use bottles of 90.

No. 3899 – Tablets ATACAND HCT 32–25 mg, are pink, oval, biconvex, non-film-coated tablets, scored on both sides and coded with ACD on one side. They are supplied as follows:

NDC 0186-0324-54 unit of use bottles of 90.

Storage:

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Keep container tightly closed.

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Made in Sweden

AstraZeneca The AstraZeneca logo, which consists of a stylized 'A' and 'Z' intertwined.