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TABLETS

ATACAND HCT™ 16-12.5

(candesartan cilexetil – hydrochlorothiazide)

ATACAND HCT™ 32-12.5

(candesartan cilexetil – hydrochlorothiazide)

USE IN PREGNANCY

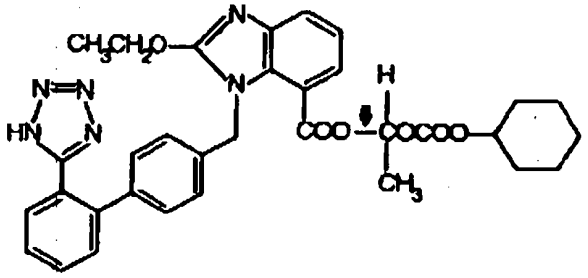
When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. When pregnancy is detected, ATACAND HCT should be discontinued as soon as possible. See WARNINGS, Fetal/Neonatal Morbidity and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

DESCRIPTION

ATACAND HCT* (candesartan cilexetil-hydrochlorothiazide) combines an angiotensin II receptor (type AT_1) antagonist and a diuretic, hydrochlorothiazide.

Candesartan cilexetil, a nonpeptide, is chemically described as (±)-1-[[(cyclohexyloxy)carbonyl]oxy]ethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-benzimidazole-7-carboxylate.

Its empirical formula is $C_{33}H_{34}N_6O_6$, and its structural formula is

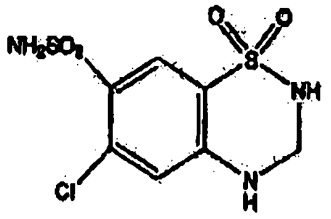


♦ site of ester hydrolysis.

*Trademark of the AstraZeneca Group of Companies

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 $C_7H_8ClN_3O_4S_2$ 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.

ATACAND HCT is available for oral administration in two 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. The inactive ingredients of the tablets are calcium carboxymethylcellulose, 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 tablet 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 AT_1 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 AT_2 receptor found in many tissues, but AT_2 is not known to be associated with cardiovascular homeostasis. Candesartan has much greater affinity (>10,000-fold) for the AT_1 receptor than for the AT_2 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 AT_1 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 ^{14}C-labeled candesartan cilexetil, approximately 33% of radioactivity is recovered in urine and approximately 67% in feces. Following an intravenous dose of ^{14}C-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/1.73m^2) 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

No differences in the pharmacokinetics of candesartan were observed in patients with mild to moderate chronic liver disease. 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 noninsulin-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. 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.

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).

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

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

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.

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.

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.

Hydrochlorothiazide

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

Alcohol, barbiturates, or narcotics – Potentiation of orthostatic hypotension may occur.

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

Other antihypertensive drugs – Additive effect or potentiation.

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

Corticosteroids, ACTH – Intensified electrolyte depletion, particularly hypokalemia.

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

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

Lithium –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

Candesartan Cilexetil – Hydrochlorothiazide

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, alone or in combination with hydrochlorothiazide, 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. In addition, candesartan (the active metabolite) was not genotoxic in the microbial mutagenesis, mammalian cell mutagenesis, and *in vitro* and *in vivo* chromosome aberration assays. In the *in vitro* Chinese hamster lung cell chromosomal aberration and mouse lymphoma assays, mutagenic effects were detected when hydrochlorothiazide was tested in the presence of candesartan. Hydrochlorothiazide was not genotoxic *in vitro* in the Ames test for point mutations and 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 for hydrochlorothiazide in the *in vitro* CHO Sister Chromatid Exchange (clastogenicity) and in the Mouse Lymphoma Cell (mutagenicity) assays and in the *Aspergillus nidulans* non-disjunction assay.

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.

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.

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: 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, are peach, oval, biconvex, non-film-coated tablets, coded ACS on one side and 162 on the other. They are supplied as follows:

NDC 0186-0162-28 unit dose packages of 100.
NDC 0186-0162-31 unit of use bottles of 30.
NDC 0186-0162-54 unit of use bottles of 90.
NDC 0186-0162-82 bottles of 1000.

No. 3826 — Tablets ATACAND HCT 32-12.5, are yellow, oval, biconvex, non-film-coated tablets, coded ACJ on one side and 322 on the other. They are supplied as follows:

NDC 0186-0322-28 unit dose packages of 100.
NDC 0186-0322-31 unit of use bottles of 30.
NDC 0186-0322-54 unit of use bottles of 90.
NDC 0186-0322-82 bottles of 1000.

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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