

WARNING: FETAL TOXICITY

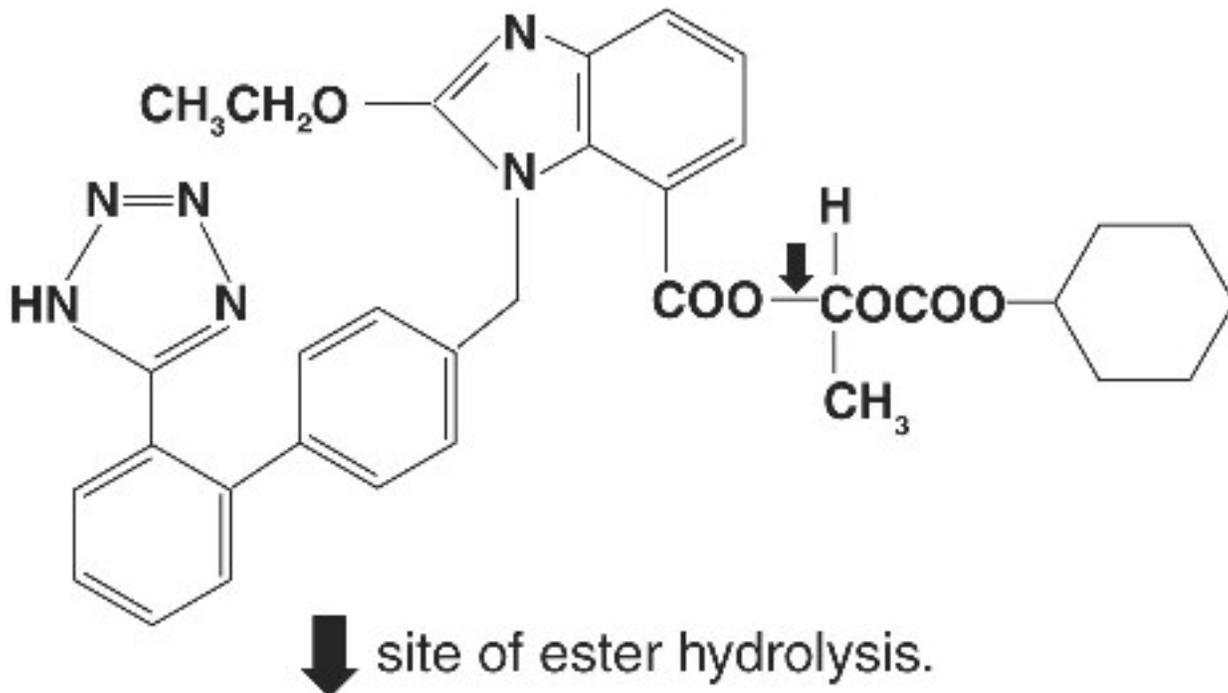
- When pregnancy is detected, discontinue candesartan cilexetil and hydrochlorothiazide tablets as soon as possible.
- Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus. See Warnings: Fetal Toxicity

DESCRIPTION

Candesartan Cilexetil and Hydrochlorothiazide Tablets combines an angiotensin II receptor (type AT₁) antagonist and a diuretic, hydrochlorothiazide.

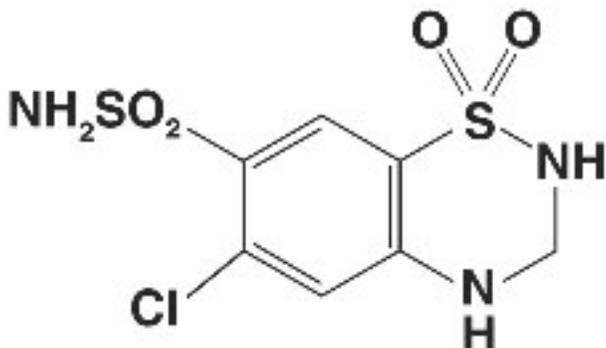
Candesartan cilexetil, a nonpeptide, is chemically described as (±)-1-Hydroxyethyl 2-ethoxy-1-[p-(*o*-1*H*-tetrazol-5-ylphenyl)benzyl]-7-benzimidazolecarboxylate, cyclohexyl carbonate (ester).

Its empirical formula is C₃₃H₃₄N₆O₆, and its structural formula is



Candesartan cilexetil is a white to off-white powder with a molecular weight of 610.66. 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, odorless, crystalline powder with a molecular weight of 297.72, which is slightly soluble in water, but freely soluble in sodium hydroxide solution, in *n*-butylamine, and in dimethyleformamide, sparingly soluble in methanol, insoluble in ether, in chloroform, and in dilute mineral acids.

Candesartan cilexetil and hydrochlorothiazide tablets are available for oral administration in two tablet strengths of candesartan cilexetil and hydrochlorothiazide.

Candesartan cilexetil and hydrochlorothiazide tablets, 16 mg/12.5 mg contain 16 mg of candesartan cilexetil and 12.5 mg of hydrochlorothiazide. Candesartan cilexetil and hydrochlorothiazide tablets, 32 mg/12.5 mg contain 32 mg of candesartan cilexetil and 12.5 mg of hydrochlorothiazide. The inactive ingredients of the tablets are lactose monohydrate, corn starch, hydroxypropyl cellulose, carboxymethyl cellulose calcium, triacetin, magnesium stearate, and ferric oxide yellow. Ferric oxide red is added only to the 16/12.5 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 to 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 candesartan cilexetil tablets at a lower dose, such as 8 mg. If a lower starting dose is selected for candesartan cilexetil, candesartan cilexetil and hydrochlorothiazide tablets are 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 to 18/8 to 11 mm Hg at doses of 16 mg/12.5 mg and 32 mg/12.5 mg. The placebo corrected trough to peak ratio was evaluated in a study of candesartan cilexetil and hydrochlorothiazide 32 mg/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

Candesartan cilexetil and hydrochlorothiazide tablets are indicated for the treatment of hypertension. This fixed dose combination is not indicated for initial therapy (see DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

Candesartan cilexetil and hydrochlorothiazide tablets are 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 Toxicity

Pregnancy Category D

Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Resulting oligohydramnios can be associated with fetal lung hypoplasia and skeletal deformations. Potential neonatal adverse effects include skull hypoplasia, anuria, hypotension, renal failure, and death.

When pregnancy is detected, discontinue candesartan cilexetil and hydrochlorothiazide tablets as soon as possible. These adverse outcomes are usually associated with use of these drugs in the second and third trimester of pregnancy. Most epidemiologic studies examining fetal abnormalities after exposure to antihypertensive use in the first trimester have not distinguished drugs affecting the renin-angiotensin system from other antihypertensive agents. Appropriate management of maternal hypertension during pregnancy is important to optimize outcomes for both mother and fetus.

In the unusual case that there is no appropriate alternative to therapy with drugs affecting the renin-angiotensin system for a particular patient, apprise the mother of the potential risk to the fetus. Perform serial ultrasound examinations to assess the intra-amniotic environment. If oligohydramnios is observed, discontinue candesartan cilexetil and hydrochlorothiazide tablets, unless it is considered lifesaving for the mother. Fetal testing may be appropriate, based on the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury. Closely observe infants with histories of in utero exposure to candesartan cilexetil and hydrochlorothiazide tablets for hypotension, oliguria, and hyperkalemia. (see **PRECAUTIONS, Pediatric Use.**)

Candesartan Cilexetil and 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]¹). For rats, the maximum dose of candesartan cilexetil was 100 mg/kg/day (about 31 times the MRHD¹). For rabbits, the maximum dose of candesartan cilexetil was 1 mg/kg/day (a maternally toxic dose that is about half the MRHD¹). In each of these studies, hydrochlorothiazide was tested at the same dose level (10 mg/kg/day, about 4, 8, and 15 times the MRHD¹ 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.

¹Doses compared on the basis of body surface area. MRHD considered to be 32 mg for candesartan cilexetil and 12.5 mg for hydrochlorothiazide.

Hypotension in Volume- and Salt-Depleted Patients

Based on adverse events reported from all clinical trials of candesartan cilexetil and hydrochlorothiazide tablets, 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 candesartan cilexetil-hydrochlorothiazide, 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 candesartan cilexetil and hydrochlorothiazide tablets

16 mg/12.5 mg or 32 mg/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 exposure to candesartan cilexetil and hydrochlorothiazide tablets during pregnancy. Discuss treatment options with women planning to become pregnant. Patients should be asked to report pregnancies to their physicians as soon as possible.

Symptomatic Hypotension

A patient receiving candesartan cilexetil and hydrochlorothiazide tablets 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, candesartan cilexetil and hydrochlorothiazide tablets 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 candesartan cilexetil and hydrochlorothiazide tablets 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.

Non-Steroidal Anti-Inflammatory Agents including Selective Cyclooxygenase-2 Inhibitors (COX-2 Inhibitors)

In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, co-administration of NSAIDs, including selective COX-2 inhibitors, with angiotensin II receptor antagonists, including candesartan, may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible. Monitor renal function periodically in patients receiving candesartan and NSAID therapy.

The antihypertensive effect of angiotensin II receptor antagonists, including candesartan may be attenuated by NSAIDs including selective COX-2 inhibitors.

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 candesartan cilexetil and hydrochlorothiazide tablets.

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 candesartan cilexetil and hydrochlorothiazide tablets 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.

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

Neonates with a history of in utero exposure to Candesartan Cilexetil and Hydrochlorothiazide Tablets:

If oliguria or hypotension occurs, direct attention toward support of blood pressure and renal perfusion. Exchange transfusions or dialysis may be required as a means of reversing hypotension and/or substituting for disordered renal function.

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Of the total number of subjects in all clinical studies of candesartan cilexetil and hydrochlorothiazide tablets (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

Candesartan cilexetil and hydrochlorothiazide tablets have 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 candesartan cilexetil and hydrochlorothiazide tablets were 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 to 32 mg) and hydrochlorothiazide (doses of 6.25 to 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 candesartan cilexetil and hydrochlorothiazide tablets and that were more frequent for candesartan cilexetil and hydrochlorothiazide tablets 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 candesartan cilexetil and hydrochlorothiazide tablets 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 candesartan cilexetil and hydrochlorothiazide tablets 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 candesartan cilexetil and hydrochlorothiazide tablets.

Creatinine, Blood Urea Nitrogen—Minor increases in blood urea nitrogen (BUN) and serum creatinine were observed infrequently. One patient was discontinued from candesartan cilexetil and hydrochlorothiazide tablets 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 candesartan cilexetil and hydrochlorothiazide tablets, but were rarely of clinical importance.

Potassium—A small decrease (mean decrease of 0.1 mEq/L) was observed in patients treated with candesartan cilexetil and hydrochlorothiazide tablets. In placebo-controlled trials, hypokalemia was reported in 0.4% of patients treated with candesartan cilexetil and hydrochlorothiazide tablets 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. Candesartan cilexetil and hydrochlorothiazide tablets 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 candesartan cilexetil and hydrochlorothiazide tablets 16 mg/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 candesartan cilexetil and hydrochlorothiazide tablets 16 mg/12.5 mg and serum potassium may improve.

A patient whose blood pressure is not controlled on 32 mg of candesartan cilexetil Tablets can expect incremental blood pressure effects from candesartan cilexetil and hydrochlorothiazide tablets 32 mg/12.5 mg. The maximal antihypertensive effect of any dose of candesartan cilexetil and hydrochlorothiazide tablets can be expected within 4 weeks of initiating that dose.

Patients with Renal Impairment: The usual regimens of therapy with Candesartan Cilexetil and Hydrochlorothiazide Tablets 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 Candesartan Cilexetil and Hydrochlorothiazide Tablets are not recommended.

Patients with Hepatic Impairment: The usual regimens of therapy with candesartan cilexetil and hydrochlorothiazide tablets may be followed in patients with mild hepatic impairment. In patients with moderate hepatic impairment, consideration should be given to initiation of candesartan cilexetil tablets at a lower dose, such as 8 mg. If a lower starting dose is selected for candesartan cilexetil tablets, candesartan cilexetil and hydrochlorothiazide tablets are 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 candesartan cilexetil and hydrochlorothiazide tablets.

Candesartan cilexetil and hydrochlorothiazide tablets may be administered with other antihypertensive agents.

Candesartan cilexetil and hydrochlorothiazide tablets may be administered with or without food.

HOW SUPPLIED

Candesartan Cilexetil and Hydrochlorothiazide Tablets, 16 mg/12.5 mg, are peach, capsule shaped, scored, biconvex, non-film coated tablets, engraved "APO" with notch on one side and "16" bisect "12.5" on the other side. They are supplied as follows:

NDC 60505-3758-9 bottles of 90.

NDC 60505-3758-5 bottles of 500.

Candesartan Cilexetil and Hydrochlorothiazide Tablets, 32 mg/12.5 mg, are yellow, capsule shaped, scored, biconvex, non-film coated tablets, engraved "APO" with notch on one side and "32" bisect "12.5" on the other side. They are supplied as follows:

NDC 60505-3759-9 bottles of 90.

NDC 60505-3759-5 bottles of 500.

Storage: Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

Manufactured by:

Apotex Research Pvt. Ltd.

India

Manufactured for:

Apotex Corp.

Weston, Florida

33326

Apotex Corp.

Candesartan Cilexetil and Hydrochlorothiazide Tablets,

16 mg/12.5 mg, 32 mg/12.5 mg

Revised: October 2012

Rev: 1

PRINCIPAL DISPLAY PANEL-16 MG/12.5 MG

Representative sample of labeling (see **HOW SUPPLIED** section for complete listing):

APOTEX CORP. NDC 60505-3758-9

Candesartan and hydrochlorothiazide Tablets

16 mg/12.5 mg

Rx only

90 tablets

*Each tablet contains 16 mg candesartan cilexetil and 12.5 mg hydrochlorothiazide.

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

Usual dosage:
See package insert

90 Tablets

NDC 60505-3758-9

**Candesartan
Cilexetil and
Hydrochlorothiazide
Tablets**

16 mg/12.5 mg*

Manufactured by:
Apotex Research Pvt. Ltd,
Bangalore-560 099, India
Code No.
KRL DRUGS/KTK/25/521/2006
Manufactured for:
Apotex Corp.,
Weston, Florida 33326



3 60505-37589-9

326556

Rx Only

APOTEX CORP.

PRINCIPAL DISPLAY PANEL-32 MG/12.5 MG

Representative sample of labeling (see **HOW SUPPLIED** section for complete listing):

APOTEX CORP. NDC 60505-3759-9

Candesartan and hydrochlorothiazide Tablets

32 mg/12.5 mg

Rx only

90 tablets

*Each tablet contains 32 mg candesartan cilexetil and 12.5 mg hydrochlorothiazide.

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

Usual dosage:
See package insert

90 Tablets

NDC 60505-3759-9

**Candesartan
Cilexetil and
Hydrochlorothiazide
Tablets**

32 mg/12.5 mg*

Manufactured by:
Apotex Research Pvt. Ltd,
Bangalore-560 099, India
Code No.
KRL DRUGS/KTK/25/521/2006
Manufactured for:
Apotex Corp.,
Weston, Florida 33326



3 60505-37599-8

326528

Rx Only

APOTEX CORP.