

Candesartan cilexetil + Hydrochlorothiazide

Candez[®] Plus

16 mg/12.5 mg Tablet

angiotensin II receptor blocker / diuretic / antihypertensive

FORMULATION

Each tablet contains:

Candesartan cilexetil.....	16 mg
Hydrochlorothiazide	12.5 mg

PRODUCT DESCRIPTION

Mottled pink, round, biconvex, plain tablet

CLINICAL PHARMACOLOGY

Pharmacodynamics

A. Candesartan

Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin-converting enzyme (ACE, kininase II). It is the main pressor agent of the renin-angiotensin-aldosterone system and is important in the pathophysiology of hypertension, heart failure and other cardiovascular disorders. Major physiological effects of angiotensin II include vasoconstriction, stimulation of synthesis and release of aldosterone, regulation of salt and water homeostasis, stimulation of cell growth.

Candesartan is a nonpeptide angiotensin II receptor antagonist that selectively blocks the binding of angiotensin II to the angiotensin II subtype 1 (AT₁) receptor in many tissues such as vascular smooth muscles and the adrenal gland.

Candesartan's action is independent of the pathways for angiotensin II synthesis. It does not inhibit ACE (kininase II), which converts angiotensin I to angiotensin II and degrades bradykinin. Since there is no effect on the degradation of bradykinin, angiotensin II receptor antagonists are unlikely to be associated with cough. The incidence of cough was lower in patients taking candesartan in studies comparing candesartan with ACE inhibitors.

Candesartan does not bind to or block other hormone receptors or ion channels significant in cardiovascular regulation. Angiotensin II receptor antagonism results in dose-related increases in plasma renin levels, angiotensin I and angiotensin II levels, and a decrease in plasma aldosterone concentration.

In hypertension, candesartan produces a dose-dependent, long-lasting reduction in arterial blood pressure. This is due to decreased systemic peripheral resistance, without reflex increase in heart rate. After discontinuation of treatment, there is no indication of rebound hypertension.

In multiple-dose studies in 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, no change in the level of HbA_{1c} was observed in patients with non-insulin-dependent (type 2) diabetes mellitus and hypertension.

Candesartan decreases systemic vascular resistance and pulmonary capillary wedge pressure, increases plasma renin activity and angiotensin II concentration, and decreases aldosterone levels in patients with chronic heart failure (CHF) and depressed left ventricular systolic function. In patients with CHF not receiving ACE inhibitors, orally administered candesartan cilexetil 8 to 16 mg once daily for up to 43 weeks significantly increased angiotensin II levels, had varying

effects on the levels of atrial natriuretic factor and pro-atrial natriuretic peptide and, in combination with enalapril, transiently decreased aldosterone levels.

B. Hydrochlorothiazide

Hydrochlorothiazide (HCTZ), a thiazide diuretic, increases the excretion of water by inhibiting the reabsorption of sodium and chloride ions at the distal renal tubule. The natriuretic effects are accompanied by a secondary loss of potassium and bicarbonate which can cause a mild hypokalemic, hypochloremic, metabolic alkalosis. Thiazides also decrease the elimination of calcium and uric acid. Thiazide diuretics usually do not affect normal blood pressure. When chronically administered, thiazide diuretics decrease peripheral vascular resistance. The exact mechanism responsible for lowered peripheral resistance is not known, however, excretion of urinary sodium by the kidneys is required to achieve blood pressure reduction.

Indirectly, the diuretic action of HCTZ reduces plasma volume, with consequent increases in plasma renin activity, aldosterone secretion, urinary potassium loss, and decrease in serum potassium. The renin-aldosterone link is mediated by angiotensin II, so coadministration of angiotensin II receptor antagonist tends to reverse the potassium loss associated with HCTZ.

Diuresis begins with 2 hours, peaks in about 4 hours and lasts about 6 to 12 hours after oral administration of HCTZ.

Pharmacokinetics

A. Candesartan

Candesartan cilexetil is the esterified prodrug of candesartan. After oral administration, candesartan cilexetil is rapidly and completely activated by enzymatic hydrolysis to candesartan during absorption from the gastrointestinal tract. Peak serum concentrations are observed 3 to 4 hours after oral administration. Oral bioavailability of candesartan tablet is about 15% and is not affected by food.

Plasma protein binding in humans is more than 99%, the majority of which is bound to albumin. Candesartan does not appear to penetrate red blood cells. The volume of distribution in healthy individuals is 0.13 L/kg.

Candesartan is mainly eliminated unchanged in urine and feces (via bile). It undergoes minor hepatic metabolism by O-deethylation to inactive metabolites. Approximately 26% of the dose is excreted unchanged in urine after oral administration. Candesartan's total plasma clearance is approximately 0.37 mL/min/kg and renal clearance is approximately 0.19 mL/min/kg. The terminal elimination half-life is about 9 hours.

B. Hydrochlorothiazide

HCTZ is well absorbed from the gastrointestinal tract. Oral bioavailability is approximately 65 to 75%. The drug crosses the placenta, but not the blood-brain barrier and is distributed in breast milk. It appears to be preferentially bound to red blood cells. HCTZ is not metabolized but is eliminated rapidly as unchanged drug in the urine. HCTZ's elimination half-life ranged from 5.6 to 14.8 hours when plasma levels were followed for at least 24 hours. At least 61% of the oral dose is eliminated unchanged within 24 hours.

INDICATION

For the treatment of essential hypertension where monotherapy is not sufficient.

DOSAGE AND ADMINISTRATION

General Dosing Recommendations:

- Individualize dose based on patient's requirements

- For mild hypertension: If the desired effect is not achieved with monotherapy, the patient may start with the combination therapy
- For moderate to severe hypertension: the combination therapy may be used for initial therapy
- May be taken with or without food

Usual Recommended Dose: 1 tablet once daily, or, as prescribed by a physician.

Antihypertensive effect is evident within 4 weeks after initiation of treatment.

Dosage in Special Population

Dose titration with candesartan cilexetil monotherapy is recommended before treatment with the combination therapy in the following:

Population	Recommended Initial Candesartan Dose
Elderly	4 mg once daily
Renal Impairment	Mild: 4 mg once daily Moderate: 2 mg once daily Severe: Thiazide diuretics are not recommended Loop diuretics are preferred
Hepatic Impairment	Mild to Moderate: 2 mg once daily Severe: Thiazide diuretics are not recommended

CONTRAINDICATIONS

- Hypersensitivity to any component of the product or to other sulfonamide-derivatives
- Anuria
- Gout
- Refractory hypokalemia and hypercalcemia
- Pregnant women or women desiring to be pregnant
- Breastfeeding
- Severe hepatic impairment and/or cholestasis

WARNINGS AND PRECAUTIONS

Warning: Angiotensin II receptor blockers can cause injury and even death to the developing fetus when used in pregnancy during the second and third trimesters. Discontinue candesartan as soon as possible upon detection of pregnancy.

A. Candesartan

- **Fetal/Neonatal Morbidity and Mortality:** 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 observed, 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. Discontinue candesartan as soon as possible when pregnancy is detected.

If oligohydramnios is observed, candesartan 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. However, physicians and patients should be aware that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with history 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.

- **Hypotension:** Observe caution when starting candesartan therapy. Carefully monitor blood pressure during initial dose titration or subsequent upward adjustment in candesartan dosage. Hypotension may occur during treatment in heart failure and hypertensive patients with intravascular volume depletion. Hypovolemia should be corrected.
- **Renal Artery Stenosis:** Candesartan may increase blood urea and serum creatinine in patients with bilateral renal artery stenosis or stenosis of the artery of a solitary kidney.
- **Renal Disease:** Periodically monitor serum potassium and creatinine levels in hypertensive patients with severe renal impairment during candesartan therapy.
- **Aortic and Mitral Valve Stenosis (Obstructive Hypertrophic Cardiomyopathy):** Observe caution when administering candesartan in patients suffering from hemodynamically relevant aortic or mitral valve stenosis, or obstructive hypertrophic cardiomyopathy.
- **Anesthesia and Surgery:** Hypotension due to blockage of the renin-angiotensin system may be observed in patients treated with angiotensin II antagonists during anesthesia and surgery. The use of intravenous fluids and/or vasopressors may be required in severe hypotension.
- **Hemodialysis:** Carefully titrate candesartan and monitor blood pressure in patients on hemodialysis.
- **Hyperkalemia:** Concomitant use of candesartan with potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium or other drugs that may increase potassium levels (e.g., heparin) may lead to increases in serum potassium in hypertensive patients.

Periodically monitor serum potassium in patients with heart failure during treatment with candesartan, particularly when coadministered with ACE inhibitors and potassium-sparing diuretics (e.g., spironolactone).

- **Primary Hyperaldosteronism:** Patients with primary hyperaldosteronism will not generally respond to antihypertensive drugs acting through inhibition of the renin-angiotensin-aldosterone system. Therefore, the use of candesartan is not recommended.
- **General:** Treatment with drugs that affect the renin-angiotensin-aldosterone system has been associated with acute hypotension, azotemia, oliguria or, rarely, acute renal failure in patients whose vascular tone and renal function depend predominantly on the activity of this system (e.g., patients with severe congestive heart failure or underlying renal

disease, including renal artery stenosis). As with any antihypertensive agent, excessive hypotension in patients with ischemic cardiopathy or ischemic cerebrovascular disease could result in a myocardial infarction or stroke.

B. Hydrochlorothiazide

- **Fluid/Electrolyte Imbalance:** Patients should be observed for clinical signs of fluid or electrolyte imbalance (e.g., volume depletion, hyponatremia, hypochloremic alkalosis, hypomagnesemia, or hypokalemia) which may occur during intercurrent diarrhea or vomiting. Serum electrolytes should be monitored regularly.

Signs and symptoms of fluid and electrolyte imbalance include dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, confusion, seizures, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances including nausea and vomiting.

- **Renal Disease:** Use with caution in patients with renal disease resulting in severe renal impairment because HCTZ decreases glomerular filtration rate and may precipitate azotemia.
- **Hepatic Disease:** Use with caution in patients with hepatic disease or progressive liver disease since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.
- **Hypersensitivity Reaction:** Hypersensitivity reactions to HCTZ 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:** Exacerbation or activation of systemic lupus erythematosus has been associated with the use of thiazide diuretics.
- **Metabolic and Endocrine Effects:**
Thiazide therapy may impair glucose tolerance. Dosage adjustment of antidiabetic agents, including insulin, may be required.

Thiazides may decrease urinary calcium excretion and may cause intermittent and slight elevation of serum calcium. Marked hypercalcemia may be evidence of hidden hyperparathyroidism. Discontinue thiazides before taking parathyroid function test.

Thiazide diuretic therapy may increase cholesterol and triglyceride levels.

Hyperuricemia may occur or acute gout may be precipitated in certain patients taking thiazide therapy.

C. Candesartan-HCTZ

- **Hypotension in Volume- and Salt-depleted Patients:** Excessive blood pressure reduction was rarely observed in patients with uncomplicated hypertension taking candesartan-HCTZ combination. Symptomatic hypotension may be observed after starting antihypertensive therapy in patients with intravascular volume- and salt-depletion (e.g., patients on dialysis or treated vigorously with diuretics). These conditions should be corrected before taking candesartan-HCTZ or treatment should be under the strict supervision of a physician.

INTERACTIONS WITH OTHER MEDICAMENTS

A. Candesartan

- Concomitant use of candesartan with lithium may cause an increase in serum lithium concentrations. Monitor serum lithium levels during concomitant use.
- Candesartan administration to patients under diuretic therapy may enhance antihypertensive effect. Start candesartan at a lower dose.
- Candesartan's antihypertensive effect may be enhanced by other antihypertensives.
- The antihypertensive effect of angiotensin II receptor antagonists may be reduced when coadministered with non-steroidal anti-inflammatory drugs (NSAIDs) such as selective COX-2 inhibitors, aspirin (>3g/day), and nonselective NSAIDs.
- Concurrent administration of angiotensin II receptor antagonists and NSAIDs may result in an increased risk of worsening of renal function (including possible acute renal failure) and an increase in serum potassium, particularly in patients with poor pre-existing renal function. The combination should be administered with caution, especially in the elderly. Regularly monitor renal function after initiation of concomitant therapy and adequately hydrate patients.
- In studies, coadministration of candesartan with other drugs such as glibenclamide, nifedipine, digoxin, warfarin, HCTZ, and oral contraceptives showed no significant drug interactions. Since 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.

B. Hydrochlorothiazide

Administration of the following drugs may interact with thiazide diuretics:

- **Alcohol, barbiturates, or narcotics:** Potentiation of orthostatic hypotension may be observed
- **Amantadine:** Increased risk of adverse effects
- **Anticholinergic agents (e.g., atropine, biperidine):** May increase availability of thiazide diuretics by decreasing gastrointestinal motility and stomach emptying rate
- **Antidiabetic medicines (oral agents and insulin):** Dosage adjustment of the antidiabetic drug may be necessary
- **Other antihypertensive drugs:** Additive effect
- **Cholestyramine and colestipol resins:** HCTZ absorption is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind HCTZ and reduce its absorption from the gastrointestinal tract by up to 85% and 43%, respectively
- **Corticosteroids, ACTH:** Intensified electrolyte depletion, particularly hypokalemia
- **Cytotoxic agents:** Decreased renal excretion; increased myelosuppressive effects
- **Pressor amines (e.g. adrenaline):** Possible decreased response to pressor amines but not sufficient to prevent their use
- **Skeletal muscle relaxants, nondepolarising (e.g. tubocurarine):** Possible increased responsiveness to the muscle relaxant
- **Lithium:** Volume depletion increases lithium absorption and may cause lithium toxicity, unless levels are closely monitored and dosage reduced accordingly. Conversely, sudden stopping of diuretic treatment may result in a sub-therapeutic level of circulating lithium
- **Non-steroidal anti-inflammatory drugs (NSAIDs) including COX-2 Inhibitors:** The administration of NSAIDs including selective COX-2 inhibitors can reduce the diuretic, natriuretic and antihypertensive effects of diuretics in some patients

STATEMENT ON USAGE FOR HIGH-RISK GROUPS

Pregnancy

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

Lactation

It is not known whether candesartan is distributed in human milk. Discontinue breastfeeding or drug due to potential risk to breastfeeding infants, taking into consideration the importance of the drug to the mother.

Use in the Elderly

There were no notable differences in efficacy or the incidence of adverse events between older and younger patients.

Use in Children

Safety and effectiveness in children have not been established.

UNDESIRABLE EFFECTS

A. Candesartan

The following undesirable effects have been reported:

Body as a Whole: Asthenia, back pain, chest pain, fatigue, fever, malaise, peripheral edema

Cardiovascular: Hypotension, tachycardia, palpitation, angina pectoris, myocardial infarction

Gastrointestinal: Nausea, abdominal pain, diarrhea, dyspepsia, vomiting, anorexia, gastroenteritis, stomach discomfort, epigastric pain, stomatitis

Hematologic: Epistaxis, neutropenia, leukopenia, agranulocytosis, leukocytosis, eosinophilia, anemia

Liver/Biliary: Abnormal hepatic function, hepatitis, jaundice

Metabolic and Nutritional/Laboratory Values: Hyperkalemia, hyponatremia, hypertriglyceridemia, hypokalemia, proteinuria; *Elevations of the following:* total cholesterol, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), lactic dehydrogenase (LDH), gamma-glutamyl transpeptidase (γ -GTP), blood urea nitrogen (BUN), creatinine phosphokinase (CPK), liver enzymes and/or bilirubin; *Reductions of the following:* serum total protein, hemoglobin and hematocrit

Muskuloskeletal: Arthralgia, myalgia, rhabdomyolysis (rare)

Nervous System: Dizziness, headache, vertigo, paresthesia, depression, anxiety, somnolence, syncope, lightheadedness, sleepiness

Respiratory: Upper respiratory tract infections, bronchitis, coughing, dyspnea, pharyngitis, rhinitis, sinusitis

Skin: Eczema, increased sweating, pruritus, rash, angioedema, urticaria

Urinary: Renal impairment, renal failure, albuminuria, hematuria, pollakiuria

B. Hydrochlorothiazide:

The following undesirable effects have been reported:

Body as a Whole: Weakness

Cardiovascular: Hypotension including orthostatic hypotension (may be aggravated by alcohol, barbiturates, narcotics, antihypertensive drugs)

Gastrointestinal: Pancreatitis, jaundice (intrahepatic cholestatic jaundice), sialadenitis, cramping, constipation, gastric irritation, anorexia

Hematologic: Aplastic anemia, agranulocytosis, leucopenia, hemolytic anemia, thrombocytopenia

Hypersensitivity reactions: Anaphylactic reactions, necrotizing angitis (vasculitis and cutaneous vasculitis), respiratory distress including pneumonitis and pulmonary edema, photosensitivity, purpura, urticaria

Metabolic and Nutritional: Electrolyte imbalance, glycosuria

Musculoskeletal: Muscle spasm

Nervous System: Restlessness

Urinary: Renal impairment, renal failure, interstitial nephritis

Skin: Erythema multiforme including Stevens-Johnson syndrome, exfoliative dermatitis including toxic epidermal necrolysis, alopecia

Urogenital: Impotence

Others: Transient blurred vision, xanthopsia

C. Candesartan-HCTZ:

The following undesirable effects have been reported:

Body as a Whole: Inflicted injury, pain, influenza-like symptoms

Cardiovascular: Extrasystoles, bradycardia, ECG abnormal

Gastrointestinal: Gastritis

Metabolic and Nutritional: Hyperuricemia, hyperglycemia, hypokalemia

Musculoskeletal: Arthrosis, arthritis, leg cramps, sciatica

Nervous System: Hypesthesia, insomnia

Skin: Dermatitis

Urinary: Urinary tract infection, cystitis

Others: Infection, viral infection, conjunctivitis, tinnitus

OVERDOSE AND TREATMENT

There is limited data on overdosage with candesartan in humans. Candesartan overdose will most likely manifest as hypotension, dizziness, and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation.

Signs and symptoms of HCTZ overdose include hypokalemia, hypochloremia, hyponatremia, dehydration resulting from excessive diuresis, dizziness, hypotension, thirst, tachycardia, ventricular arrhythmias, sedation, and muscle cramps.

Institute symptomatic treatment and monitor vital signs if symptomatic hypotension occurs. In the event of hypotension, place the patient in supine position. For severe hypotension, administer 0.9% sodium chloride injection as IV infusion to expand fluid volume.

Monitor and correct serum electrolyte and acid imbalance.

Candesartan is not removed by hemodialysis. The degree to which HCTZ is removed by hemodialysis has not been established.

CAUTION

Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

For suspected adverse drug reaction, seek medical attention immediately and report to the FDA at www.fda.gov.ph **AND** Unilab at (+632) 858-1000 or productsafety@unilab.com.ph. By reporting undesirable effects, you can help provide more information on the safety of this medicine.

AVAILABILITY

Candesartan cilexetil + Hydrochlorothiazide (Candez[®] Plus) 16 mg + 12.5 mg Tablet, in blister pack x 10s (box of 30s)

**STORE AT TEMPERATURES NOT EXCEEDING 30°C
KEEP THE PRODUCT OUT OF SIGHT AND REACH OF CHILDREN**

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