# Candesartan cilexetil

**Candez®**
**8 mg and 16 mg Tablet**
**angiotensin II receptor blocker / antihypertensive**

## FORMULATION

Each tablet contains:
Candesartan cilexetil……8 mg or 16 mg

## PRODUCT DESCRIPTION

- **8 mg Tablet :** Mottled pink, round 7/32" diameter, biconvex, plain tablet
- **16 mg Tablet :** Mottled pink, 9/32" diameter, round, bevel-edged tablet, bisected on one side and plain on the other side

## CLINICAL PHARMACOLOGY

***Pharmacodynamics***

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 ($AT_1$) 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.

Candesartan once a day provides effective and smooth blood pressure reduction over 24 hours, with little difference between maximum and trough effects during the dosing interval.

The onset of antihypertensive effect of candesartan generally occurs within 2 hours after its administration given as a single dose.

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 a day 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.

***Pharmacokinetics***
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 ($C_{max}$) 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.

**Special Population**
***Elderly:*** In the elderly (>65 years old), both $C_{max}$ and area under the concentration-time curve (AUC) of candesartan are increased by approximately 50% and 80% respectively, compared with younger individuals. However, the blood pressure response and the incidence of adverse events are similar in younger and elderly patients.

***Renal Impairment:*** In patients with mild to moderate renal impairment, $C_{max}$ and AUC of candesartan increased during repeated dosing by approximately 50% and 70%, respectively. The corresponding changes in patients with severe renal impairment were approximately 50% and 110% respectively. The terminal half-life of candesartan was approximately doubled in patients with severe renal impairment. The AUC of candesartan in patients undergoing hemodialysis was similar to that in patients with severe renal impairment.

***Hepatic Impairment:*** In patients with mild to moderate hepatic impairment, the AUC of candesartan was increased by approximately 20%. In patients with moderate to severe hepatic impairment, increase in the AUC of candesartan was approximately 80%. There is only limited experience in patients with severe hepatic impairment and/or cholestasis.

**INDICATIONS**
- Hypertension; may be used alone or in combination with other antihypertensives
- Heart failure in patients with impaired left ventricle systolic function (left ventricular ejection fraction ≤40%) to reduce cardiovascular death and to reduce heart failure hospitalizations. Candesartan also has an added effect on these outcomes when used with an ACE inhibitor.

**DOSAGE AND ADMINISTRATION**
***General Dosing Recommendations:***
- Individualize dose based on patient's requirements
- May be taken with or without food

| INDICATIONS | RECOMMENDED ORAL DOSE |
|---|---|
| **Hypertension** | **Initial Dose when used as Monotherapy in Patients who are Not Volume Depleted:** 16 mg once daily<br>➢ May be administered once or twice daily with total daily doses ranging from 8 to 32 mg |

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| | ➢ Dose should be adjusted based on blood pressure (BP) response<br>➢ If BP control is not achieved with a 32 mg dose, alternative strategies should be considered<br><br>**Initial Dose in Patients with Intravascular Volume Depletion:** 4 mg once daily<br><br>**Dosage in Elderly Patients:** Lower dose should be considered<br><br>**Dosage in Patients with Renal Impairment:**<br>Mild: 4 mg once daily<br>Moderate: 2 mg once daily<br>Severe: Not recommended<br><br>**Dosage in Patients with Hepatic Impairment:**<br>Mild to Moderate: 2 mg once daily<br>Severe: Contraindicated<br><br>May be administered with other antihypertensive drugs<br>Antihypertensive effect is evident within 4 weeks after initiation of treatment. |
| **Heart Failure** | **Initial Dose:** 4 mg once daily<br>➢ Target dose is 32 mg once daily, which is achieved by doubling the dose at approximately 2-week intervals, as tolerated by the patient.<br><br>May be administered with other heart failure treatment (e.g., ACE inhibitors, beta-blockers, diuretics, digitalis, or a combination of these products) |
| Or as prescribed by the physician. | |

**CONTRAINDICATIONS**

- Hypersensitivity to candesartan cilexetil or to any component of the product
- Pregnancy
- Breastfeeding
- Severe hepatic impairment and/or cholestasis
- Concomitant use with aliskiren in patients with diabetes mellitus or renal impairment [glomerular filtration rate (GFR) <60 mL/min/1.73 $m^2$]

**WARNINGS AND PRECAUTIONS**

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

***Fetal Toxicity:*** The use of drugs that act on the renin-angiotensin-aldosterone 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 as soon as possible. These adverse outcomes are usually associated with use of these drugs in the second and third trimesters 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-aldosterone 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-aldosterone system for a particular patient, the mother should be informed of the potential

risk to the fetus. Perform serial ultrasound examinations to assess the intra-amniotic environment. If oligohydramnios is observed, discontinue candesartan, unless it is considered lifesaving for the mother. Fetal testing may be appropriate, based on the week of pregnancy. However, physicians and patients should be aware that oligohydramnios may not appear until after the fetus has sustained irreversible injury. Closely observe infants with histories of *in utero* exposure to candesartan for hypotension, oliguria and hyperkalemia.

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 a 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.

***Use in Heart Failure***
Triple combination of candesartan with an ACE inhibitor and a mineralocorticoid receptor antagonist in heart failure is not recommended. Closely monitor blood pressure, renal function and electrolytes in patients receiving candesartan and other agents that affect the renin-angiotensin-aldosterone system.

***Renal Impairment***
As with other agents inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in some individuals treated with candesartan.

Periodically monitor serum potassium and creatinine levels in hypertensive patients with severe renal impairment during candesartan therapy.

***Hepatic Impairment***
Observe caution when administering candesartan in patients with impaired hepatic function. The elimination of candesartan may be reduced in these patients and lower doses may therefore be required.

***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-aldosterone 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.

***Renal Artery Stenosis***
Drugs affecting the renin-angiotensin-aldosterone system, including angiotensin II receptor antagonists, may increase blood urea nitrogen (BUN) and serum creatinine in patients with unilateral or bilateral renal artery stenosis.

***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 result in hyperkalemia.

Periodically monitor serum potassium during treatment with candesartan. The combination of candesartan with an ACE inhibitor and a potassium-sparing diuretic (e.g., spironolactone) in patients with heart failure is not recommended.

***Primary Hyperaldosteronism***
Patients with primary hyperaldosteronism will not generally respond to antihypertensive agents 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.

***Effects on Ability to Drive and Use Machines***
No studies have been conducted on the effects of candesartan on the ability to drive and use machines. However, dizziness or fatigue may occasionally occur when taking antihypertensives. Patients should exercise caution when driving vehicles or operating machinery.

**INTERACTIONS WITH OTHER MEDICAMENTS**

***Potassium-sparing diuretics/potassium supplements/salt substitutes:*** May increase serum potassium; thus, concomitant use is not recommended.

***Lithium:*** Reversible increases in lithium concentrations and toxicity; thus, coadministration is not recommended. If coadministration proves necessary, monitor serum lithium level carefully.

***Nonsteroidal anti-inflammatory drugs [NSAIDs, i.e., selective cyclooxygenase-2 inhibitors (COX-2) inhibitors, aspirin > 3 g/day]:*** Reduced antihypertensive effect of candesartan. 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.

***Dual Blockade of the Renin-Angiotensin-Aldosterone System (RAAS):*** Dual blockade of the RAAS with angiotensin II receptor antagonists, ACE inhibitors or aliskiren is associated with increased risk of hypotension, hyperkalemia and changes in renal function (including acute renal failure) compared with monotherapy. Closely monitor blood pressure, renal function and electrolytes in patients on candesartan and other agents that affect the RAAS.

Do not coadminister candesartan with aliskiren in patients with diabetes mellitus or renal impairment (GFR <60 mL/min/1.73 $m^2$). Avoid concomitant use of angiotensin II receptor antagonists and ACE inhibitors in patients with diabetic nephropathy.

***Antihypertensive agents (e.g., diuretic):*** Candesartan administration to patients under diuretic therapy may enhance antihypertensive effect. Start candesartan at a lower dose. Candesartan's antihypertensive effect may also be enhanced by other class of antihypertensive agents.

***Others:*** In studies, coadministration of candesartan with other drugs such as glibenclamide, nifedipine, digoxin, warfarin, hydrochlorothiazide, 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.

**STATEMENT OF USAGE IN HIGH-RISK GROUPS**

***Pregnancy: Pregnancy Category D.*** **(See Warnings and Precautions, Fetal Toxicity).**

***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.

***Children:*** The safety and efficacy of candesartan have not been established in children less than 18 years old.

***Elderly:*** There were no age-related differences in efficacy or safety profile of candesartan, but greater sensitivity of some older individuals cannot be ruled out.

**UNDESIRABLE EFFECTS**

The most frequently reported adverse effects with candesartan include back pain, dizziness, upper respiratory tract infection, pharyngitis, and rhinitis.

***Blood and lymphatic system disorders:*** Agranulocytosis, anemia, eosinophilia, leukocytosis, leukopenia, neutropenia, thrombocytopenia
***Metabolism and nutrition disorders:*** Hyperkalemia, hypoglycemia, hyponatremia, thirst
***Psychiatric disorders:*** Insomnia
***Nervous system disorders:*** Headache, lightheadedness, numbness of limbs, numbness of tongue, sleepiness, syncope, vertigo, abnormal taste
***Eye disorders:*** Abnormal vision
***Cardiac disorders:*** Atrial fibrillation, bradycardia, extrasystole, palpitation
***Vascular disorders:*** Hypotension, shock, hot flushes
***Respiratory, thoracic and mediastinal disorders:*** Cough, epistaxis, interstitial pneumonia, sinusitis
***Gastrointestinal disorders:*** Anorexia, constipation, diarrhea, epigastric pain, gastric ulcer, nausea, stomach discomfort, stomatitis, vomiting
***Hepatobiliary disorders:*** Abnormal hepatic function, hepatitis, jaundice
***Skin and subcutaneous tissue disorders:*** Angioedema, eczema, photosensitivity, pruritus, rash, urticaria
***Musculoskeletal and connective tissue disorders:*** Arthralgia, myalgia, rhabdomyolysis
***Renal and urinary disorders:*** Renal impairment, renal failure, proteinuria, pollakiuria
***General disorders and administration site conditions:*** Edema, fatigue, fever, malaise, lumbar pain, weakness
***Investigations:*** Increases in serum potassium, serum creatinine, blood urea nitrogen (BUN), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (γ-GTP), lactic dehydrogenase (LDH), creatinine phosphokinase (CPK), c-reactive protein (CRP), total cholesterol, serum uric acid; decreases in serum total protein, hemoglobin

**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.

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.

Candesartan is not removed by hemodialysis.

**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 (Candez®) 8 mg Tablet**, in blister pack x 10s (box of 30s)
**Candesartan cilexetil (Candez®) 16 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**

Manufactured by **AMHERST LABORATORIES, INC.**
UNILAB Pharma Campus, Barangay Mamplasan
Biñan, Laguna, Philippines
for **UNILAB, Inc.**
No. 66 United Street, Mandaluyong City
Metro Manila, Philippines