# Advantec™

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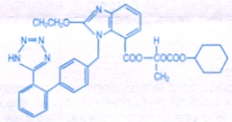
[Candesartan Cilexetil + Hydrochlorothiazide]

**TABLETS 16mg+12.5mg**

## DESCRIPTION

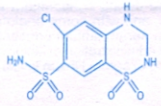
ADVANTEC (Candesartan Cilexetil+Hydrochlorothiazide) combines a subtype angiotensin II receptor (type AT1) antagonist, candesartan and a diuretic, hydrochlorothiazide. Candesartan cilexetil is a produrg hydrolyzed to candesartan during absorption from the gastrointestinal tract.

Candesartan cilexetil, a nonpeptide, is chemically described as (±)-1-Hydroxyethyl 2-ethoxy-1-[p-(o-1H-tetrazol-5-ylphenyl) benzyl]-7-benzimidazolecarboxylate, cyclohexyl carbonate (ester). Its molecular formula is $C_{33}H_{34}N_6O_6$, and the structural formula is:



Candesartan Cilexetil

Chemically hydrochlorothiazide is 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide. Its molecular formula is $C_7H_8ClN_3O_4S_2$ and its structural formula is:



Hydrochlorothiazide

## QUALITATIVE AND QUANTITATIVE COMPOSITION

ADVANTEC (Candesartan Cilexetil + Hydrochlorothiazide) is available for oral administration as:

ADVANTEC Tablets
Each tablet contains:
Candesartan Cilexetil ... 16mg
Hydrochlorothiazide USP ... 12.5mg

## CLINICAL PHARMACOLOGY

### Mechanism of Action

Candesartan Cilexetil:

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.

Candesartan cilexetil is rapidly converted to the active drug, candesartan, by ester hydrolysis during absorption from the gastrointestinal tract. Candesartan is an angiotensin II receptor antagonist, selective for AT1 receptors, with tight binding to and slow dissociation from the receptor. It has no agonist activity. 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. 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:

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 co-administration 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

*Absorption & Distribution*

Candesartan Cilexetil:

Candesartan cilexetil is rapidly and completely bioactivated by ester hydrolysis during the absorption from the gastrointestinal tract to candesartan, a selective subtype angiotensin II receptor antagonist. The volume of distribution of candesartan is 0.13 L/kg. Candesartan is highly bound to plasma ( > 99%) and does not penetrate . The binding is constant at candesartan plasma concentrations well above the range achieved with recommended doses. 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

Hydrochlorothiazide preferentially binds to red blood cells. It crosses placental barrier and distributes into breast milk. 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 & Excretion*

Candesartan Cilexetil

Candesartan undergoes minor hepatic metabolism by O-deethylation to an inactive metabolite. When candesartan is administered orally, about 26% of the dose is excreted unchanged in urine. Following an oral dose of $^{14}C$-labeled candesartan cilexetil, approximately 33% of radioactivity is recovered in urine and approximately 67% in feces. Total plasma clearance of candesartan is 0.37 mL/min/kg, with a renal clearance of 0.19 mL/min/kg. The elimination half-life of candesartan is approximately 9 hours.

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.

After single and repeated administration, the pharmacokinetics of candesartan are linear for oral doses up to 32mg of candesartan cilexetil.

### Special Populations

*Geriatric*

The pharmacokinetics of candesartan are linear in the elderly (>65 years), and candesartan and its inactive metabolite do not accumulate in the serum of these patients upon repeated, once-daily administration. No initial dosage adjustment is necessary.

*Renal Insufficiency*

In patients with renal insufficiency, serum concentrations of candesartan are elevated. After repeated dosing, the AUC and $C_{max}$ are approximately doubled in patients with severe renal impairment (creatinine clearance <30mL/min/1.73m$^2$) compared to patients with normal kidney function. The pharmacokinetics of candesartan in hypertensive patients undergoing hemodialysis is similar to those in hypertensive patients with severe renal impairment. Candesartan cannot be removed by hemodialysis. No initial dosage adjustment is necessary in patients with renal insufficiency.

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

*Hepatic Insufficiency*

No dose adjustment is recommended for patients with mild hepatic impairment. In patients with moderate hepatic impairment, consideration should be given to initiation of ADVANTEC at a lower dose, such as 8 mg. If a lower starting dose is selected for candesartan cilexetil, ADVANTEC is not recommended for initial titration because the appropriate initial starting dose of candesartan cilexetil cannot be given.Thiazide diuretics should be used with caution in patients with hepatic impairment.

## THERAPEUTIC INDICATIONS

ADVANTEC (Candesartan Cilexetil +Hydrochlorothiazide) is indicated for the treatment of hypertension. The fixed dose combination is not indicated for initial therapy.

## DOSAGE AND ADMINISTRATION

The usual starting dose of ADVANTEC (Candesartan Cilexetil + Hydrochlorothiazide) is one tablet per day with or without food. To minimize dose dependent side effects, it is usually appropriate to begin combination therapy only after a patient has failed to achieve the desired effect with monotherapy.

### Dose Titration

A patient whose blood pressure is not controlled on 25mg of hydrochlorothiazide once daily can expect an incremental effect from ADVANTEC (Candesartan Cilexetil+Hydrochlorothiazide). A patient whose blood pressure is controlled on 25mg of hydrochlorothiazide

but is experiencing decreases in serum potassium can expect the same or incremental blood pressure effects from ADVANTEC (Candesartan Cilexetil+Hydrochlorothiazide) and serum potassium may improve.

*Renal Insufficiency:*
The usual regimens of therapy with ADVANTEC (Candesartan Cilexetil+Hydrochlorothiazide) may be followed as long as the patient's creatinine clearance is >30mL/min.

*Hepatic Insufficiency:*
The usual regimens of therapy with ADVANTEC (Candesartan Cilexetil+Hydrochlorothiazide) may be followed in patients with mild hepatic impairment. In patients with moderate hepatic impairment, consideration should be given to initiation of ADVANT (Candesartan Cilexetil) at a lower dose, such as 8mg. If a lower starting dose is selected for candesartan cilexetil, ADVANTEC (Candesartan Cilexetil+Hydrochlorothiazide) is not recommended for initial titration because the appropriate initial starting dose of candesartan cilexetil cannot be given.
Thiazide diuretics should be used with caution in patient with hepatic insufficiency; therefore care should be exercised with dosing of ADVANTEC (Candesartan Cilexetil+Hydrochlorothiazide).

## ADVERSE REACTIONS
Adverse reactions with candesartan cilexetil+hydrochlorothiazide are mild and transient in nature and have only infrequently required discontinuation of therapy.
Common

Back pain, dizziness, influenza-like symptoms, headache, upper respiratory tract infection.
Less Common

Inflicted injury, fatigue, pain, chestpain, peripheral edema, asthenia vertigo, paresthesia, hypesthesia, bronchitis, sinusitis, pharyngitis, coughing, rhinitis, dyspnea, arthralgia, myalgia, arthrosis, arthritis, leg cramps, sciatica, nausea, abdominal pain, diarrhea, dyspepsia, gastritis, gastroenteritis, vomiting, hyperuricemia, hyperglycemia, hypokalemia, increased BUN, creatine phosphokinase increased, urinary tract infection, hematuria, cystitis, abnormal hepatic function, increased transaminase levels, tachycardia, palpitation, extrasystoles, bradycardia, abnormal ECG,, eczema, sweating increased, pruritus, dermatitis, rash, epistaxis, infection, viral infection, conjunctivitis, tinnitus.
Rare

Angina pectoris, myocardial infarction and angioadema.

## CONTRAINDICATIONS
The combination of candesartan cilexetil and hydrochlorothiazide is contraindicated

- In patients who are hypersensitive to this drug or any component of this product.
- In patients with anuria or hypersensitivity to other sulfonamide-derived drugs, due to hydrochlorothiazide component in the preparation.

## WARNING / PRECAUTIONS

**USE IN PREGNANCY**
When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. When pregnancy is detected, ADVANTEC should be discontinued as soon as possible unless it is considered life saving for the mother.

*Hypotension in Volume- and Salt-Depleted Patients*
In patients with an activated renin-angiotensin system, such as volume and/ or salt-depleted patients (eg, those being treated with diuretics), symptomatic hypotension may occur. These conditions should be corrected prior to administration of ADVANTEC, or the treatment should start under close medical supervision.

Candesartan Cilexetil:
*Impaired Renal Function*
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 rennin-angiotensin-aldosterone system (e.g, patient 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.

Hydrochlorothiazide:
*- Impaired Hepatic Function*
Thiazide diuretics should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

*- Impaired Renal Function*
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.

*- Hypersensitivity Reaction*
Hypersensitivity reactions to hydrochlorothiazide may occur in patients with or without a history of allergy or bronchial asthma.

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

- Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals.
- Thiazides may decrease urinary calcium excretion. They 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.

**Nursing Mothers**
Hydrochlorothiazide is excreted in breast milk but it is not known whether candesartan is excreted 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.

**Drug Interactions**
Candesartan Cilexetil
There are no significant drug interactions of Candesartan Cilexetil given with other drugs such as glyburide, nifedipine, digoxin, warfarin, hydrochlorothiazide, and oral contraceptives. Because candesartan is not siginificantly metabolized by the cytrochrome P450 system and at therapeutic concentrations has no effect on P450 enzymes, interactions with drugs that inhibit or are metabolized by those enzmes would not be expected.

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

Hydrochlorothiazide
When administered concurrently the following drugs may interact with thiazide diuretics:
*Alcohol, barbiturates, or narcotics* – Potentiation of orthostatic hypotension may occur.
*Antidiabetic drugs (oral agents and insulin)* – Dosage adjustment of the antidiabetic drug may be required.
*Other antihypertensive drugs* – Additive effect or potentiation.
*Cholestyramine and colestipol resins* – Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85 and 43 percent, respectively.
*Corticosteroid, 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.
*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 ADVANTEC 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.

## STORAGE
Store at 25°C (Excursions permitted between 15°C to 30°C)
Protect from sunlight and moisture.
The expiration date refers to the product correctly stored at the required conditions.

## HOW SUPPLIED
ADVANTEC (Candesartan Cilexetil + Hydrochlorothiazide) Tablets 16mg+12.5mg are available in blister packs of 28's.

**Keep out of the reach of children.**

**To be sold on prescription of a registered medical practitioner only.**

**Please read the contents carefully before use.**
**This package insert is continually updated from time to time.**

Manufactured by:

Getz pharma (PVT) LIMITED
www.getzpharma.com
29-30/27, K.I.A., Karachi, Pakistan

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