Advant™

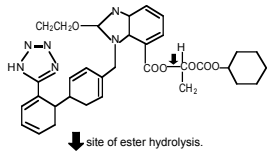
[Candesartan Cilexetil]

8mg, 16mg TABLETS

DESCRIPTION

ADVANT (Candesartan cilexetil), a prodrug, is hydrolyzed to candesartan during absorption from the gastrointestinal tract. Candesartan is a selective AT_1 subtype angiotensin II receptor antagonist.

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



(Candesartan Cilexetil)

QUANTITATIVE & QUALITATIVE COMPOSITION

ADVANT (Candesartan cilexetil) is available for oral administration as:

1. ADVANT Tablets 8mg
   Each tablet contains:
   Candesartan cilexetil 8mg

2. ADVANT Tablets 16mg
   Each tablet contains:
   Candesartan cilexetil 16mg

CLINICAL PHARMACOLOGY

Mechanism of Action

Candesartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT_1 receptor in many tissues, such as vascular smooth muscle and the adrenal gland. Its action is, therefore, independent of the pathways for angiotensin II synthesis.

There is also an AT_2 receptor found in many tissues, but AT_2 is not known to be associated with cardiovascular homeostasis. Candesartan has much greater affinity (>10,000-fold) for the AT_1 receptor than for the AT_2 receptor.

Blockade of the renin-angiotensin system with ACE inhibitors, which inhibit the biosynthesis of angiotensin II from angiotensin I, is widely used in the treatment of hypertension. ACE inhibitors also inhibit the degradation of bradykinin, a reaction also catalyzed by ACE. Because candesartan does not inhibit ACE (kininase II), it does not affect the response to bradykinin. 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.

Pharmacokinetics

Absorption:

Candesartan cilexetil is rapidly and completely bioactivated by ester hydrolysis during absorption from the gastrointestinal tract to candesartan, a selective AT_1 subtype angiotensin II receptor antagonist.

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.

Metabolism:

Candesartan undergoes minor hepatic metabolism by O-deethylation to an inactive metabolite.

Distribution:

After single and repeated administration, the pharmacokinetics of candesartan are linear for oral doses up to 32mg of candesartan cilexetil. Candesartan and its inactive metabolite do not accumulate in serum upon repeated once-daily dosing.

The volume of distribution of candesartan is 0.13L/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.

Excretion

When candesartan is administered orally about 26% of the dose is excreted unchanged in urine. Total plasma clearance of candesartan is 0.37mL/min/kg, with a renal clearance of 0.19mL/min/kg. The elimination half-life of candesartan is approximately 9 hours.

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) and in both sexes. 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 with 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.

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 <30mL/min/1.73m^2) compared to patients with normal kidney function. The pharmacokinetics of candesartan in hypertensive patients undergoing hemodialysis are similar to those in hypertensive patients with severe renal impairment. Candesartan cannot be removed by hemodialysis. No initial dosage adjustment is necessary in patients with mild renal insufficiency.

Hepatic Insufficiency

The pharmacokinetics of candesartan were compared in patients with mild and moderate hepatic impairment to matched healthy volunteers following a single oral dose of 16mg candesartan cilexetil. The increase in AUC for candesartan was 30% in patients with mild hepatic impairment (Child-Pugh A) and 145% in patients with moderate hepatic impairment (Child-Pugh B). The increase in C_{max} for candesartan was 56% in patients with mild hepatic impairment and 73% in patients with moderate hepatic impairment. The pharmacokinetics after candesartan cilexetil administration have not been investigated in patients with severe hepatic impairment.

THERAPEUTIC INDICATIONS

ADVANT (Candesartan cilexetil) is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents.

DOSAGE AND ADMINISTRATION

ADVANT (Candesartan cilexetil) may be administered with or without food. Dosage must be individualized. Blood pressure response is dose related over the range of 2 to 32mg. The usual recommended starting dose of ADVANT (Candesartan cilexetil) is 16mg once daily when it is used as monotherapy in patients who are not volume depleted. ADVANT (Candesartan cilexetil) can be administered once or twice daily with total daily doses ranging from 8mg to 32mg. Larger doses do not appear to have a greater effect, and there is relatively little experience with such doses. Most of the antihypertensive effect is present within 2 weeks, and maximal blood pressure reduction is generally obtained within 4 to 6 weeks of treatment with ADVANT (Candesartan cilexetil).

If blood pressure is not controlled by ADVANT (Candesartan cilexetil) alone, a diuretic may be added. ADVANT (Candesartan cilexetil) may be administered with other antihypertensive agents.

Hepatic impaired patients:

In patients with moderate hepatic impairment, consideration should be given to initiation of ADVANT (Candesartan cilexetil) at a lower dose. No initial dose adjustment is necessary in patients with mild hepatic impairment.

Volume depleted patients

For patients with possible depletion of intravascular volume (e.g., patients treated with diuretics, particularly those with impaired renal function), consideration should be given to initiation of ADVANT (Candesartan cilexetil) at a lower dose.

ADVERSE REACTIONS

In general, treatment with candesartan cilexetil was well tolerated. However, the adverse effects reported with candesartan are usually mild and transient including headache and dizziness.

Potentially important adverse events that have been reported, whether or not attributed to treatment, with an incidence of 0.5% cannot be determined whether these events were causally related to candesartan cilexetil.

Body as a Whole: asthenia, fever;
Central and Peripheral Nervous System: paresthesia, vertigo;
Gastrointestinal System Disorder: dyspepsia, gastroenteritis;
Heart Rate and Rhythm Disorders: tachycardia, palpitation;
Metabolic and Nutritional Disorders: creatinine phosphokinase increased, hyperglycemia, hypertriglyceridemia, hyperuricemia;
Musculoskeletal System Disorders: myalgia;
Platelet/Bleeding-Clotting Disorders: epistaxis;
Psychiatric Disorders: anxiety, depression, somnolence;
Respiratory System Disorders: dyspnea;
Skin and Appendages Disorders: rash, sweating increased;
Urinary System Disorders: hematuria.

Other reported events seen less frequently included angina pectoris, myocardial infarction, and angioedema. Adverse events occurred at about the same rates in men and women, older and younger patients, and black and non black patients.

Following adverse effects are rarely reported:
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: pruritis and urticaria.

CONTRAINDICATIONS

Candesartan cilexetil is contraindicated in patients who are hypersensitive to this drug or any component of this product.

WARNINGS / 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, candesartan cilexetil should be discontinued as soon as possible.

Hypotension in Volume- and Salt-Depleted Patients

In patients with an activated renin-angiotensin system, such as volume and/or salt-depleted patients (e.g., those being treated with diuretics), symptomatic hypotension may occur. These conditions should be corrected prior to administration of candesartan cilexetil, or the treatment should start under close medical supervision. 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.

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. Caution should be made while using this medication.

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.

Nursing Mothers

It is not known whether candesartan is excreted in human milk but 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

- 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.
- 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.
- Since both, ACE inhibitors and angiotensin receptor blockers, can increase the concentrations of potassium in the blood, other medications that can increase the concentration of potassium in the blood, such as *spironolactone*, and *potassium supplements*, should be used cautiously with candesartan.
- 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.

Overdosage

The most likely manifestation 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 instituted. Candesartan cannot be removed by hemodialysis.

STORAGE

Store below 30°C.
Protect from sunlight and moisture.
The expiration date refers to the product correctly stored at the required conditions.

HOW SUPPLIED

ADVANT (Candesartan cilexetil) 8mg tablets are available in alu-alu blister packs of 14's.
ADVANT (Candesartan cilexetil) 16mg tablets are available in alu-alu blister packs of 14's & 28's.

Keep out of 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.

Getz pharma (PVT) LIMITED
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