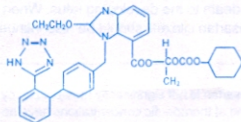


TABLETS 8mg, 16mg

DESCRIPTION

ADVANT (Candesartan cilexetil), a prodrug, is hydrolyzed to candesartan during absorption from the gastrointestinal tract. Candesartan is a selective AT₁ subtype angiotensin II receptor antagonist.

Candesartan cilexetil, a nonpeptide, is chemically described as (±)-1-Hydroxyethyl 2-ethoxy-1- β -(α -1*H*-tetrazol-5-ylphenyl)benzyl]-7-benzimidazolecarboxylate, cyclohexyl carbonate (ester). Its molecular formula is C₃₃H₃₄N₆O₆, 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

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.

Pharmacokinetics

Absorption and distribution

Following oral administration, candesartan cilexetil is converted to the active substance candesartan. The absolute bioavailability of candesartan is approximately 40% after an oral solution of candesartan cilexetil. The estimated absolute bioavailability of the tablet is therefore 14%. The mean peak serum concentration (C_{max}) is reached 3-4 hours following tablet intake. The candesartan serum concentrations increase linearly with increasing doses in the therapeutic dose range. No gender related differences in the pharmacokinetics of candesartan have been observed. The area under the serum concentration versus time curve (AUC) of candesartan is not significantly affected by food.

Candesartan is highly bound to plasma protein (more than 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. The apparent volume of distribution of candesartan is 0.1 L/kg.

Metabolism and excretion:

Candesartan is mainly eliminated unchanged via urine and bile and only to a minor extent eliminated by hepatic metabolism. The terminal half-life of candesartan is approximately 9 hours. There is no accumulation following multiple doses. Total plasma clearance of candesartan is about 0.37 mL/min/kg, with a renal clearance of about 0.19 mL/min/kg. The renal elimination of Candesartan is both by glomerular filtration and active tubular

secretion. Following an oral dose of C-labelled candesartan cilexetil, approximately 26% of the dose is excreted in the urine as candesartan and 7% as an inactive metabolite while approximately 56% of the dose is recovered in the faeces as candesartan and 10% as the inactive metabolite. 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.

Special Populations

Pediatrics

In children 1 to 17 years of age, plasma levels are greater than 10-fold higher at peak (approximately 4 hours) than 24 hours after a single dose. Children 1 to < 6 years of age, given 0.2 mg/kg had exposure similar to adults given 8 mg.

Children > 6 years of age had exposure similar to adults given the same dose.

Geriatrics

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 upon repeated, once-daily administration.

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 insufficiency (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 insufficiency. Candesartan cannot be removed by hemodialysis.

In heart failure patients with renal insufficiency, AUC 0-72h was 36% and 65% higher in mild and moderate renal insufficiency, respectively. C_{max} was 15% and 55% higher in mild and moderate renal insufficiency, respectively.

Hepatic Insufficiency

The increase in AUC for candesartan was 30% in patients with mild hepatic insufficiency (Child-Pugh A) and 145% in patients with moderate hepatic insufficiency (Child-Pugh B). The increase in C_{max} for candesartan was 56% in patients with mild hepatic insufficiency and 73% in patients with moderate hepatic insufficiency.

THERAPEUTIC INDICATIONS

Hypertension

ADVANT (Candesartan cilexetil) is indicated for the treatment of hypertension in adults and children 1 to < 17 years of age. It may be used alone or in combination with other antihypertensive agents.

Heart Failure

ADVANT (Candesartan cilexetil) is indicated for the treatment of heart failure (NYHA class II-IV) in adults with left ventricular systolic dysfunction (\leq 40%) to reduce cardiovascular death and to reduce heart failure hospitalizations. ADVANT (Candesartan cilexetil) also has an added effect on these outcomes when used with an ACE inhibitor.

DOSE AND ADMINISTRATION

Hypertension

Adults

Dosage must be individualized. Response is dose related over the range of 2 to 32 mg. The usual recommended starting dose of ADVANT (Candesartan cilexetil) is 16 mg 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 8 mg to 32 mg. 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). ADVANT (Candesartan cilexetil) may be administered with or without food.

Pediatrics

ADVANT (Candesartan cilexetil) may be administered once daily or divided into two equal doses. Adjust the dosage according to blood pressure response. For patients with possible depletion of intravascular volume (e.g., patients treated with diuretics, particularly those with impaired renal function), initiate ADVANT (Candesartan cilexetil) under close medical supervision

and consider administration of a lower dose.

Children 1 to <6 years of age:

The dose range is 0.05 to 0.4 mg/kg per day. The recommended starting dose is 0.20 mg/kg.

Children 6 to <17 years of age:

For those less than 50 kg, the dose range is 2 to 16 mg per day. The recommended starting dose is 4 to 8 mg.

For those greater than 50 kg, the dose range is 4 to 32 mg per day. The recommended starting dose is 8 to 16 mg.

An antihypertensive effect is usually present within 2 weeks, with full effect generally obtained within 4 weeks of treatment with ADVANT (Candesartan cilexetil).

Children < 1 year of age must not receive ADVANT (Candesartan cilexetil) for hypertension.

Heart Failure

The recommended initial dose for treating heart failure is 4 mg once daily. The target dose is 32 mg once daily, which is achieved by doubling the dose at approximately 2-week intervals, as tolerated by the patient.

ADVERSE REACTIONS

Adult Hypertension

In general, treatment with ADVANT was well tolerated. The most common adverse reaction was headache and dizziness. The adverse reaction that occurred very rarely include back pain, upper respiratory tract infection, pharyngitis and rhinitis.

The other potentially important adverse reactions observed includes; *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*: creatine 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, increased sweating. *Urinary System Disorders*: hematuria.

The other reported adverse reactions observed less frequently included angina pectoris, myocardial infarction and angioedema.

Pediatric Hypertension

Among children treated for hypertension were observed to experience worsening renal diseases. The association between candesartan and exacerbation of the underlying condition could be excluded.

Heart Failure

The adverse reaction observed in adults heart patients receiving total daily doses upto 32mg resulted small increase in serum creatinine (mean increase 0.2 mg/dL), serum potassium (mean increase 0.15 mEq/L), small decrease in hemoglobin (mean decrease 0.5 gm/dL) and hematocrit (mean decrease 1.6%) were observed.

CONTRAINDICATIONS

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

WARNINGS / PRECAUTIONS

General

As with any antihypertensive agent, excessive blood pressure decrease in patients with ischaemic cardiopathy or ischaemic cerebrovascular disease could result in a myocardial infarction or stroke.

Hypotension

Hypotension may occur during treatment with candesartan in heart failure patients. It may also occur in hypertensive patients with intravascular volume depletion. Caution should be observed when initiating therapy and correction of hypovolaemia should be attempted.

Renal artery stenosis

Candesartan may increase blood urea and serum creatinine in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney.

Hemodialysis

During dialysis the blood pressure may be particularly sensitive to AT₁-receptor blockade as a result of reduced plasma volume and activation of the renin-angiotensin-aldosterone system. Therefore, candesartan should be carefully titrated with thorough monitoring of blood pressure in patients on haemodialysis.

Aortic and mitral valve stenosis

Special caution is indicated in patients suffering from haemodynamically relevant aortic or mitral valve stenosis, or obstructive hypertrophic

cardiomyopathy.

Anaesthesia and surgery

Hypotension may occur during anaesthesia and surgery in patients treated with angiotensin II antagonists due to blockage of the renin-angiotensin system.

Nursing Mothers

It is unknown 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.

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.

Drug Interactions

- Because candesartan is not significantly metabolized by the cytochrome P450 system and at therapeutic concentrations have no effects on P450 enzymes, interactions with drugs that inhibit or are metabolized by these enzymes would not be expected.
- No significant drug interactions have been reported with candesartan cilexetil when given with other drugs such as glyburide, nifedipine, digoxin, warfarin, hydrochlorothiazide, and oral contraceptives or given with enalapril to patients with heart failure (NYHA class II and class III).
- The antihypertensive effect of candesartan may be enhanced by other medicinal products with blood pressure lowering properties, concomitant use of potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium, or other medicinal products that may increase potassium levels (e.g. heparin) may lead to increase in serum potassium in hypertensive patients.
- 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 and careful monitoring of serum lithium levels is recommended during concomitant use.
- Concomitant use of Angiotensin II receptor antagonists and NSAIDs may lead to an increased risk of worsening of renal function, including possible acute renal failure, and an increase in serum potassium, especially in patients with poor pre-existing renal function. The combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring renal function after initiation of concomitant therapy, and periodically thereafter.

Overdose

The main manifestation of an overdose is likely to be symptomatic hypotension and dizziness. In individual case reports of overdose (of up to 672 mg candesartan cilexetil), patient recovery was uneventful. If symptomatic hypotension should occur, symptomatic treatment should be instituted and vital signs monitored. The patient should be placed supine with the legs elevated. If this is not sufficient, plasma volume should be increased by infusion of, for example, isotonic saline solution. Symptomimetic medicinal products may be administered if the above-mentioned measures are not sufficient. Candesartan is not removed by haemodialysis.

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

ADVANT (Candesartan cilexetil) Tablets 8mg are available in blister pack of 14's.

ADVANT (Candesartan cilexetil) Tablets 16mg are available in blister pack of 14'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.

Manufactured by:

 **Getz**
pharma
(PVT) LIMITED
www.getzpharma.com

29-30/27,
K.I.A., Karachi,
Pakistan

Rev. Jun 10
L02-200004323