SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF DRUG PRODUCT

Advant Tablets 16mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains:
Candesartan Cilexetil …… 16mg

3. PHARMACEUTICAL FORM

White colored, square shaped tablet, bisect line on one side and plain on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Advant (Candesartan Cilexetil) is indicated for the treatment of:

- Hypertension.
- Hypertension with intravascular volume depletion.
- Heart failure with impaired left ventricular systolic function when ACE inhibitors are not tolerated and heart failure with impaired left ventricular systolic function in conjunction with an ACE inhibitor (under expert supervision).

4.2 Posology and Method of Administration

Hypertension Adult:
Initially 8mg once daily, increased if necessary up to 32mg once daily, doses to be increased at intervals of 4 weeks; usual dose 8mg once daily.
Hypertension with intravascular volume depletion Adult:
Initially 4mg once daily, increased if necessary up to 32mg daily, doses to be increased at intervals of 4 weeks; usual dose 8mg once daily.
Heart failure with impaired ventricular systolic function when ACE inhibitors are not tolerated and heart failure with impaired left ventricular systolic function in conjunction with an ACE inhibitor (under expert supervision)
Adult: Initially 4mg once daily, increased at intervals of at least 2 weeks to 'target' dose of 32mg once daily or to maximum tolerated dose.

4.3 Contraindications:

- Hypersensitivity to Candesartan Cilexetil or to any of the excipient of product.
- Severe hepatic impairment and/or cholestasis.
- The concomitant use of Candesartan Cilexetil with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60ml/min/1.73m^2).

4.4 Special warnings and special precautions for use

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.

4.5 Interaction with other medicaments

- 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

4.6 Fertility, pregnancy and lactation

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.

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.

Fertility

No adequate data available.

4.7 Effects on ability to drive and operate machines

Some people may feel tired or dizzy when taking Candesartan. If this happens to you, do not drive or use any tools or machines.

4.8 Undesirable effects

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.

4.9 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.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic Group: Angiotensin II Receptor Antagonist (ARB)
ATC Code: C09CA06

5.1 Pharmacodynamic properties

Mechanism of Action:
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. There is also an AT2 receptor found in many tissues, but AT2 is not known to be associated with cardiovascular homeostasis. Candesartan has much greater affinity (>10,000-fold) for the AT1 receptor than for the AT2 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

5.2 Pharmacokinetic Properties

Absorption:
Candesartan Cilexetil is rapidly and completely bioactivated by ester hydrolysis during absorption from the gastrointestinal tract to candesartan, a selective AT1 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 (Cmax) is reached after 3 to 4 hours. Food with a high fat content does not affect the bioavailability of candesartan after Candesartan Cilexetil administration.

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.

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

Elimination:
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 (Cmax 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 Cmax 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 Cmax 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

5.3 Preclinical Safety Data

There was no evidence of abnormal systemic or target organ toxicity at clinically relevant doses**.**

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

- Lactose Monohydrate
- Pharmacoat 606 (HPMC)
- Polysorbate 80
- Carboxy Methyl Cellulose Calcium
- Magnesium Stearate

6.2 Incompatibilities

Not applicable

6.3 Shelf-life

3 Years

6.4 Special precautions for storage

- Store below 30°C.
- Protect from sunlight & moisture.
- The expiration dates refer to the product correctly stored in the required conditions.

6.5 Nature and contents of container

ADVANT (Candesartan Cilexetil) 16mg tablets are available in Alu-Alu blister packs of 14's.

6.6 Special precautions for disposal

No special requirements.

6.7 Instructions for use/handling

- Keep out of reach of children.
- To be sold on prescription of a registered medical practitioner only.

7. MARKETING AUTHORISATION HOLDER

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8. DATE OF REVISION OF THE TEXT

Nil

8. PRODUCT REGISTRATION NUMBER

034070

9. DATE OF PRODUCT REGISTRATION ISSUED

Oct 24, 2004