

AUSTRALIAN PRODUCT INFORMATION

ADESAN

Candesartan cilexetil tablets



1 NAME OF THE MEDICINE

Candesartan cilexetil

2 & 3 QUALITATIVE AND QUANTITATIVE COMPOSITION AND PHARMACEUTICAL FORM

- Adesan 4 mg: Contains 4 mg of candesartan cilexetil as the active ingredient.
A white to off white round, biconvex tablet debossed with M on left side of the breakline and C on the right side of the breakline on one side of the tablet and 24 on the other side.
- Adesan 8 mg: Contains 8 mg of candesartan cilexetil as the active ingredient.
A mottled pink, round, biconvex tablet debossed with M on left side of the breakline and C on right side of the breakline on one side of the tablet and 25 on the other side.
- Adesan 16 mg: Contains 16 mg of candesartan cilexetil as the active ingredient.
A mottled pink, round, biconvex tablet debossed with M on left side of the breakline and C on right side of the breakline on one side of the tablet and 31 on the other side.
- Adesan 32 mg: Contains 32 mg of candesartan cilexetil as the active ingredient.
A mottled pink, round, biconvex tablet debossed with MC above the breakline and 32 below the break line on one side of the tablet and plain on the other side.

ADESAN also contains sugars (as lactose).

For the full list of excipients, see section 6.1 LIST OF EXCIPIENTS.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Treatment of hypertension.

Treatment of patients with heart failure and impaired left ventricular systolic function (left ventricular ejection fraction $\leq 40\%$) as add-on therapy to ACE inhibitors or when ACE inhibitors are not tolerated.

4.2 DOSE AND METHOD OF ADMINISTRATION

Candesartan should be taken once daily with or without food.

Paediatrics

The safety and efficacy of candesartan have not been established in children.

Hypertension

The recommended maintenance dose of candesartan is 8 mg or 16 mg once daily. The maximal antihypertensive effect is attained within 4 weeks following initiation of treatment. For those patients who start on 8 mg and require further blood pressure reduction, a dose increase to 16 mg is

recommended. An initial dose of 16 mg is also well tolerated. Some patients may receive an additional benefit by increasing the dose to 32 mg once daily.

In patients with less than optimal blood pressure reduction on candesartan, combination with a thiazide diuretic is recommended.

Geriatrics

An initial dose of 8 mg is recommended.

Hepatic Insufficiency

Dose titration is recommended in patients with mild to moderate chronic liver disease and a lower initial dose of 4 mg should be considered. ADESAN should not be used in patients with severe hepatic impairment and/or cholestasis (see section 4.3 CONTRAINDICATIONS).

Renal Insufficiency

No initial dosage adjustment is necessary in patients with mild to moderate impaired renal function (i.e. creatinine clearance 30-80 mL/min/1.73m² BSA). In patients with severely impaired renal function (i.e. creatinine clearance <30 mL/min/1.73m² BSA) including patients on haemodialysis a lower initial dose of 4 mg should be considered.

Heart failure

The usual recommended initial dose of candesartan is 4 mg once daily. Up-titration to the target dose of 32 mg once daily or the highest tolerated dose is performed by doubling the dose at intervals of at least 2 weeks (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Special patient populations

No initial dose adjustment is necessary for elderly patients or in patients with renal or hepatic impairment.

Concomitant therapy

Candesartan can be administered with other heart failure treatment, including ACE inhibitors, beta-blockers, diuretics and digitalis or a combination of these medicines (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).and section 5.1 pharmacodynamic properties).

4.3 CONTRAINDICATIONS

Hypersensitivity to any component of ADESAN.

Pregnancy and lactation (see section 4.6 FERTILITY, PREGNANCY AND LACTATION).

Severe hepatic impairment and/or cholestasis.

The use of ADESAN in combination with aliskiren-containing medicines in patients with diabetes mellitus (type I or II) or with moderate to severe renal impairment (GFR<60ml/min/1.73m²).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

General

In patients whose vascular tone and renal function depend predominantly on the activity of the renin-angiotensin-aldosterone system (e.g. patients with severe congestive heart failure or underlying renal disease, including renal artery stenosis), treatment with drugs that affect this system has been associated with acute hypotension, azotaemia, oliguria or, rarely, acute renal failure. As with any antihypertensive agent, an excessive blood pressure decrease in patients with ischaemic cardiopathy or ischaemic cerebrovascular disease could result in a myocardial infarction or stroke.

Kidney Transplantation

There is limited clinical experience regarding the administration of candesartan in patients who have undergone renal transplant.

Renal Artery Stenosis

Other drugs that affect the renin-angiotensin-aldosterone system, i.e. angiotensin converting enzyme (ACE) inhibitors, may increase blood urea and serum creatinine in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney. A similar effect may be anticipated with angiotensin II receptor antagonists.

Aortic and Mitral Valve Stenosis or Obstructive Hypertrophic Cardiomyopathy

As with other vasodilators, special caution is indicated in patients suffering from haemodynamically relevant aortic or mitral valve stenosis, or obstructive hypertrophic cardiomyopathy.

Primary Hyperaldosteronism

Patients with primary hyperaldosteronism will not generally respond to antihypertensive drugs acting through inhibition of the renin-angiotensin-aldosterone system. Therefore, the use of candesartan in these patients is not recommended.

Hypotension

Hypotension may occur during treatment with candesartan in heart failure patients. As described for other agents acting on the renin-angiotensin-aldosterone system, it may also occur in hypertensive patients with intravascular volume depletion. Caution should be observed when initiating therapy and correction of hypovolemia should be attempted.

Dual Blockade of the Renin-Angiotensin-Aldosterone System (RAAS) with Aliskiren-containing Medicines

There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure). Dual blockade of the renin-angiotensin-aldosterone system through the combined use of candesartan cilexetil with an ACE-inhibitor or aliskiren is therefore not recommended (see section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS)

If dual blockade therapy is considered necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure.

ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy. The use of ADESAN with aliskiren is contraindicated in patients with diabetes mellitus (type I or II) or moderate to severe renal impairment ($GFR < 60 \text{ml/min/1.73m}^2$) (see SECTION 4.3 CONTRAINDICATIONS).

Use in heart failure

Triple combination of candesartan with an ACE-inhibitor and a mineralocorticoid receptor antagonist used in heart failure is also not recommended. Use of these combinations should be under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure.

Hyperkalaemia

Based on experience with the use of other drugs that affect the renin-angiotensin aldosterone system, 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, trimethoprim/sulfamethoxazole) may lead to increases in serum potassium in hypertensive patients. In heart failure patients treated with candesartan, hyperkalaemia may occur. During treatment with candesartan in patients with heart failure, periodic monitoring of serum potassium is recommended,

especially when taken concomitantly with ACE inhibitors and potassium-sparing diuretics such as spironolactone.

Haemodialysis

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 (see section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Anaesthesia and Surgery

Hypotension may occur during anaesthesia and surgery in patients treated with angiotensin II antagonists due to blockade of the renin-angiotensin system. Very rarely, hypotension may be severe such that it may warrant the use of intravenous fluids and/or vasopressors.

Combination use of ACE inhibitors or angiotensin receptor antagonists, anti-inflammatory drugs and thiazide diuretics

The use of an ACE inhibiting drug (ACE-inhibitor or angiotensin receptor antagonist), an anti-inflammatory drug (NSAID or COX-2 inhibitor) and a thiazide diuretic at the same time increases the risk of renal impairment. This includes use in fixed-combination products containing more than one class of drug. Combined use of these medications should be accompanied by increased monitoring of serum creatinine, particularly at the institution of the combination. The combination of drugs from these three classes should be used with caution particularly in elderly patients or those with pre-existing renal impairment.

Use in Hepatic Impairment

There is limited clinical experience in patients with severe hepatic impairment and/or cholestasis. Use in patients with severe hepatic impairment is contraindicated. Caution is advised in patients with mild to moderate hepatic impairment. There have been reports of clinically significant liver disease occurring with other angiotensin II receptor antagonists. No such cases have been reported to date with candesartan.

Use in Renal Impairment

As with other agents inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible patients treated with candesartan. When candesartan is used in hypertensive patients with severe renal impairment, periodic monitoring of serum potassium and creatinine levels should be considered. There is very limited experience in patients with very severe or end-stage renal impairment (i.e. creatinine clearance <15 ml/min/1.73 m² BSA). Evaluation of patients with heart failure should include periodic assessments of renal function. During dose titration of candesartan, monitoring of serum creatinine and potassium is recommended.

Use in the Elderly

There are special dosage recommendations for use of candesartan cilexetil in elderly patients (see section 4.2 DOSE & METHOD OF ADMINISTRATION).

Paediatric Use

Safety and efficacy have not been established in children.

Effects on Laboratory Tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Dual blockade of the renin-angiotensin-aldosterone system (RAAS) with aliskiren-containing medicines

The combination of ADESAN with aliskiren-containing medicine is contraindicated in patients with diabetes mellitus (type I or II) or moderate to severe renal impairment ($GFR < 60 \text{ ml/min/1.73m}^2$) and is not recommended in other patients. Clinical trial data has shown that dual blockade of the RAAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting agent (see section 4.3 CONTRAINDICATIONS and 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Food

Food increases the rate of absorption of candesartan however, the extent of absorption of candesartan is not affected by food.

Lithium

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors. A similar effect may occur with angiotensin II receptor antagonists (AIIRAs) and careful monitoring of serum lithium levels is recommended during concomitant use.

Other drugs

Compounds which have been investigated in clinical pharmacokinetic studies include hydrochlorothiazide, warfarin, digoxin, oral contraceptives (i.e. ethinylestradiol/levonorgestrel), glibenclamide and nifedipine and enalapril. No pharmacokinetic interactions of clinical significance were identified in these studies.

The antihypertensive effect of angiotensin II receptor antagonists, including candesartan, may be attenuated by NSAIDs, including COX-2 inhibitors and acetylsalicylic acid.

As with ACE inhibitors, concomitant use of AIIRAs 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 older patients and in volume depleted patients. Patients should be adequately hydrated and consideration should be given to monitoring renal function after initiation of concomitant therapy and periodically thereafter.

Candesartan is eliminated only to a minor extent by hepatic metabolism (CYP2C9). Available interaction studies indicate no effect on CYP2C9 and CYP3A4 but the effect on other cytochrome P450 isoenzymes is presently unknown.

Candesartan may be administered with other antihypertensive agents.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

Candesartan cilexetil had no adverse effects on the reproductive performance of male or female rats at oral doses up to 300 mg/kg/day.

Use in Pregnancy

Pregnancy Category: Category D

Category D: Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

The use of candesartan cilexetil is contraindicated during pregnancy (see section 4.3 CONTRAINDICATIONS). Patients receiving candesartan cilexetil should be made aware of that before contemplating a possibility of becoming pregnant so that they can discuss appropriate options with their treating physician. When pregnancy is diagnosed, treatment with candesartan cilexetil must be stopped immediately and if appropriate, alternative therapy should be started.

Drugs that act on the renin-angiotensin system (RAS) can cause fetal and neonatal morbidity and death when administered to pregnant women. Exposure to angiotensin II receptor antagonist therapy is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia).

Use in Lactation

It is not known whether candesartan is excreted in human milk. However, candesartan is excreted in the milk of lactating rats. Because of the potential for adverse effects on the nursing infant, breastfeeding should be discontinued if the use of candesartan cilexetil is considered essential.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

When driving vehicles or operating machines, it should be taken into account that dizziness or weariness may occur during treatment.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Hypertension

Candesartan was well tolerated in clinical studies showing an adverse event profile comparable to that of placebo. Generally adverse events were mild and transient. The overall incidence of adverse effects showed no association with dose, age or gender. Withdrawals from treatment due to adverse events were similar with candesartan cilexetil (3.1%) and placebo (3.2%).

Information on adverse events was obtained from 39 Phase I to Phase III clinical studies, involving a total of 5,464 subjects. Candesartan was administered as mono or combination therapy to 2,061 hypertensive patients. The crude frequency of the most commonly occurring adverse events, irrespective of causality, reported for those patients and the 573 placebo comparators are given below.

Table 1: The crude frequency of the most commonly occurring adverse events

Adverse Event	Monotherapy Studies		Combination Studies		
	Placebo (n=573)	Candesartan (n=1388)	Placebo (n=205)	Candesartan (n=444)	Candesartan + HCTZ (n=673)
Cardiovascular					
peripheral oedema	0.7	1.3	1.0	1.6	0.1
Gastrointestinal					
nausea	1.4	2.2	0.5	1.1	1.0
abdominal pain	1.9	1.7	2.0	1.4	1.2
diarrhoea	2.3	1.6	1.5	0.9	0.7

vomiting	1.0	1.2	-	-	-
Musculo-skeletal					
back pain	1.2	4.0	1.0	2.3	2.4
Nervous system					
headache	10.7	10.9	4.9	4.1	1.7
dizziness	2.6	2.7	2.0	1.6	2.2
Other					
influenza-like symptoms	1.0	1.9	0.5	0.9	1.8
inflicted injury	0.9	1.7	-	-	-
fatigue	1.6	1.5	-	-	-
Respiratory					
URTI	3.9	6.1	2.0	2.3	1.0
bronchitis	2.6	1.9	2.0	0.7	0.9
coughing	1.8	1.9	2.0	1.1	0.9
pharyngitis	0.7	1.9	-	-	-
rhinitis	0.5	1.3	-	1.1	0.6

HCTZ = hydrochlorothiazide

Median (mean) duration of exposure: placebo 57 (68 days) and candesartan cilexetil: 56 (78 days).

Laboratory Findings

In general, there were no clinically important influences of candesartan cilexetil on routine laboratory variables. As for other inhibitors of the renin-angiotensin-aldosterone system, small decreases in haemoglobin have been seen. Increases in creatinine, urea or potassium and decreases in sodium have been observed. In clinical trials, elevations of ALT occurred in 1.3% of candesartan-treated patients and 0.5% of those treated with placebo. The incidence of AST elevation was 0.4% with candesartan and 0% with placebo. No routine monitoring of laboratory variables is usually necessary for patients receiving candesartan. However, in patients with severe renal impairment, periodic monitoring of serum potassium and creatinine levels should be considered.

Heart Failure

The adverse experience profile of candesartan in heart failure patients was consistent with the pharmacology of the drug and the health status of the patients. In the CHARM clinical program, comparing candesartan in doses up to 32 mg (n=3,803) to placebo (n=3,796), 21.0% of the candesartan cilexetil group and 16.1% of the placebo group discontinued treatment because of adverse events. Adverse reactions commonly ($\geq 1/100$, $< 1/10$) seen were:

Vascular disorders:

Hypotension

Metabolism and nutrition disorders:

Hyperkalaemia

Renal and urinary disorders:

Renal impairment

Laboratory findings:

Increases in creatinine, urea and potassium. Periodic monitoring of serum creatinine and potassium is recommended (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Post-Marketing

The following adverse reactions have been reported very rarely (<0.01%) in post marketing experience:

Blood and lymphatic system disorders:

Leukopenia, neutropenia and agranulocytosis

Metabolism and nutrition disorders:

Hyperkalaemia, hyponatraemia

Hepato-biliary disorders:

Increased liver enzymes, abnormal hepatic function or hepatitis

Skin and subcutaneous tissue disorders:

Angioedema, rash, urticaria, pruritus

Musculoskeletal, connective tissue and bone disorders:

Back pain, myalgia

Renal and urinary disorders:

Renal impairment, including renal failure in susceptible patients (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Rare reports of rhabdomyolysis have been reported in patients receiving angiotensin II receptor blockers.

Although causality to candesartan has not been established, the following neuropsychiatric and cardiovascular adverse reactions have been very rarely reported during post-marketing surveillance. These were: agitation, anxiety, depression, insomnia, somnolence, nervousness, nightmare, sleep disorder and palpitations.

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE**Symptoms**

Based on pharmacological considerations, the main manifestation of an overdose is likely to be symptomatic hypotension and dizziness. In single case reports of overdose (up to 672 mg candesartan cilexetil) patient recovery was uneventful.

Management

If symptomatic hypotension should occur, symptomatic treatment should be instituted and vital signs monitored. The patients should be placed supine with the legs elevated. If this is not sufficient, plasma volume should be increased by the infusion of, for example, isotonic saline solution. Sympathomimetic drugs may be administered if the above-mentioned measures are not sufficient.

Candesartan is not removed by haemodialysis.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

Angiotensin II is the primary vasoactive hormone of the renin-angiotensin-aldosterone system and plays a significant role in the pathophysiology of hypertension, heart failure and other cardiovascular disorders. It also has an important role in the pathogenesis of end organ hypertrophy and damage. The major physiological effects of angiotensin II, such as vasoconstriction, aldosterone stimulation, regulation of salt and water homeostasis and stimulation of cell growth, are mediated via the type 1 (AT₁) receptor.

Candesartan cilexetil is a prodrug suitable for oral use. It 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.

Candesartan does not inhibit angiotensin converting enzyme (ACE), which converts angiotensin I to angiotensin II and degrades bradykinin. Since there is no effect on ACE and no potentiation of bradykinin or substance P, angiotensin II receptor antagonists are unlikely to be associated with cough. This has been confirmed in controlled clinical studies with candesartan. Candesartan does not bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

In hypertension, candesartan causes a dose-dependent, long-lasting reduction in arterial blood pressure. The antihypertensive action is due to decreased systemic peripheral resistance, while heart rate, stroke volume and cardiac output are not affected. There is no indication of serious or exaggerated first dose hypotension or rebound effect after cessation of treatment.

Candesartan is effective in hypertension. After administration of a single dose, onset of antihypertensive effect generally occurs within two hours. With continuous treatment, the maximum reduction in blood pressure with any dose is generally attained within four weeks and is sustained during long-term treatment. It provides effective and smooth blood pressure reduction over the 24 hours dosing interval, with a trough/peak ratio confirming once daily dosing.

Candesartan can be used as monotherapy, or in combination with other antihypertensive drugs, such as thiazide diuretics, calcium antagonists and lisinopril, for improved blood pressure control. Age and gender have no influence on the efficacy of candesartan.

Candesartan has favourable renal haemodynamic effects. It increases renal blood flow and maintains or increases glomerular filtration rate while renal vascular resistance and filtration fraction are reduced. Candesartan reduces urinary protein excretion in hypertensive patients with microalbuminuria or nephropathy of different aetiology. Candesartan has no adverse effect on blood glucose or lipid profile. In a variety of preclinical safety studies conducted in several species, expected exaggerated pharmacological effects (e.g. renal changes leading to juxtaglomerular cell hypertrophy, adrenal gland zona glomerulosa atrophy and reduced heart weight related to reduced afterload), due to modification of the renin-angiotensin-aldosterone system homeostasis, have been observed. The incidence and severity of the effects induced were dose and time related and have been shown to be reversible in adult animals. Fetotoxicity has been observed in late pregnancy (see section 4.6 FERTILITY, PREGNANCY AND LACTATION).

Clinical Trials

Hypertension

The Candesartan and Lisinopril Microalbuminuria (CALM) study was a 24-week double blind, parallel group trial (n=199) to evaluate the effects of candesartan and lisinopril alone and in combination on urinary albumin excretion (UAE) in patients with type II diabetes mellitus, hypertension and microalbuminuria. Patients were randomly allocated to four treatment regimens: 1) 24 weeks of candesartan monotherapy (1/3 of the patients); 2) 24 weeks of lisinopril monotherapy (1/3 of the patients); 3) 12 weeks of candesartan monotherapy, followed by 12 weeks of candesartan + lisinopril combination therapy (1/6 of the patients); and 4) 12 weeks of lisinopril monotherapy, followed by 12 weeks of lisinopril + candesartan combination therapy (1/6 of the patients). Thus, after 12 weeks, half of the patients were treated with candesartan monotherapy (n=99) and half with lisinopril monotherapy (n=98). After 24 weeks, 1/3 of the patients still in the study were on candesartan monotherapy (n=49), 1/3 on lisinopril monotherapy (n=46), and 1/3 on combination therapy (candesartan + lisinopril, n=25; lisinopril + candesartan, n=24).

Significant reduction in urinary albumin/creatinine ratio (UACR), in both monotherapy treatment groups was observed, although no significant difference between treatment groups was seen. Combination therapy following monotherapy for 12 weeks showed significantly greater reduction in UACR (mean reduction of 50%) than candesartan cilexetil 16 mg monotherapy (mean reduction in UACR 24%) and numerically greater reduction than lisinopril 20 mg monotherapy (mean reduction in UACR 39%).

All treatment regimens reduced both systolic and diastolic blood pressure significantly. The blood pressure reductions were significantly greater with combination therapy than with monotherapy, whether lisinopril was added to candesartan, or candesartan was added to lisinopril (see Table 2).

Table 2: The effects of candesartan and lisinopril alone and in combination, on blood pressure.

	Baseline		Change at 12 weeks		Change at 24 weeks	
	SBP mmHg	DBP mmHg	SBP mmHg	DBP mmHg	SBP mmHg	DBP mmHg
Candesartan 16 mg (n=49)	162	96	-15	-10	-14	-10
Lisinopril 20 mg (n=46)	161	96	-14	-10	-17	-11
Candesartan 16 mg + Lisinopril 20 mg from 12 weeks (n=25)	161	95	-16	-11	-22*	-16*
Lisinopril 20 mg + candesartan 16 mg from 12 weeks (n=24)	161	96	-14	-10	-28***	-17***

*p<0.05, ***p<0.001 for the additional blood pressure reduction at 24 weeks compared with 12 weeks

The antihypertensive effects of candesartan cilexetil and losartan potassium at their highest recommended doses administered once daily were compared in two randomised, double-blind trials. In a total of 1,268 patients with mild to moderate hypertension who were not receiving other antihypertensive therapy, candesartan cilexetil 32 mg lowered systolic and diastolic blood pressure by 2 to 3 mmHg on average more than losartan potassium 100 mg, when measured at the time of either peak or trough effect.

Heart Failure

In patients with chronic heart failure (CHF) and depressed left ventricular systolic function (left ventricular ejection fraction, LVEF \leq 40%), candesartan decreases systemic vascular resistance and pulmonary capillary wedge pressure, increases plasma renin activity and angiotensin II concentration, and decreases aldosterone levels.

Treatment with candesartan reduces mortality and hospitalisation due to CHF and improves symptoms as shown in the Candesartan in Heart failure – Assessment of Reduction in Mortality and morbidity (CHARM) program comprising 3 studies (CHARM-Alternative, CHARM-Added and CHARM-Preserved). In all 3 studies, patients on optimal baseline therapy were randomised to placebo or candesartan (titrated from 4 mg or 8 mg once daily to 32 mg once daily or the highest tolerated dose, mean dose 24 mg) and followed for a median of 37.7 months.

CHARM-Alternative

CHARM-Alternative was a multinational, randomised, double-blind placebo controlled study in CHF patients (NYHA class II-IV, n=2,028) with a LVEF \leq 40% not treated with an ACE inhibitor because of intolerance.

Table 3: The effect of candesartan versus placebo on composite endpoints and their components in CHARM-Alternative

Endpoint	Absolute risk Reduction (%)	Hazard Ratio (HR)	95% CI	Relative Risk reduction (%)
CV mortality or CHF hospitalisation	7.0	0.77	0.67-0.89, p<0.001	23
CV mortality	3.2	0.85	0.71-1.02, p=0.072	15
CHF hospitalisation	7.7	0.68	0.57-0.81, p<0.001	32
All-cause mortality or CHF hospitalisation	6.0	0.80	0.70-0.92, p=0.001	20
All-cause mortality	3.0	0.87	0.74-1.03, p=0.104	13

CHARM-Added

CHARM-Added was a multinational, randomised, double-blind placebo controlled study in CHF patients (NYHA class II-IV, n=2,548) with a LVEF \leq 40% treated with ACE inhibitors.

Table 4: The effect of candesartan versus placebo on composite endpoints and their components in CHARM-Added

Endpoint	Absolute risk Reduction (%)	Hazard Ratio (HR)	95% CI	Relative Risk Reduction (%)
CV mortality or CHF hospitalisation	4.4	0.85	0.75-0.96, p=0.011	15
CV mortality	3.6	0.84	0.72-0.98, p=0.029	16
CHF hospitalisation	3.8	0.83	0.71-0.96, p=0.013	17

All-cause mortality or CHF hospitalisation	3.9	0.87	0.78-0.98, p=0.021	13
All-cause mortality	2.8	0.89	0.77-1.02, p=0.086	11

CHARM-Preserved

CHARM-Preserved was a multinational, randomised, double-blind placebo controlled study in CHF patients (n=3,023, NYHA class II-IV) with a LVEF >40%, approximately 20% of whom received an ACE inhibitor. In the CHARM-Preserved study there was no effect of candesartan upon mortality.

Table 5: The effect of candesartan versus placebo on composite endpoints and their components in CHARM-Preserved

Endpoint	Absolute risk Reduction (%)	Hazard Ratio (HR)	95% CI	Relative Risk Reduction (%)
CV mortality or CHF hospitalisation	2.3	0.89	0.77-1.03, p=0.018	11
CV mortality	0.0	0.99	0.80-1.22, p=0.918	1
CHF hospitalisation	2.4	0.85	0.72-1.01, p=0.071	15
All-cause mortality or CHF hospitalisation	1.7	0.92	0.80-1.05, p=0.221	8
All-cause mortality	0.0	1.02	0.85-1.22, p=0.836	-

All-cause mortality was also assessed in pooled populations, CHARM-Alternative and CHARM-Added (HR 0.88, 95% CI 0.79-0.98, p=0.018) and all three studies (HR 0.91, 95% CI 0.83-1.00, p=0.055). This corresponds to a relative risk reduction of 12% and 9% respectively and an absolute risk reduction of 2.9 and 1.6% respectively.

Treatment with candesartan resulted in improved NYHA functional class in CHARM Alternative and CHARM-Added (p=0.008 and p=0.020 respectively).

The beneficial effects of candesartan on cardiovascular mortality and CHF hospitalisation were consistent irrespective of age, gender and concomitant medication. Candesartan was effective also in patients taking both beta-blockers and ACE inhibitors at the same time, and the benefit was obtained whether or not patients were taking ACE inhibitors at the target dose recommended by treatment guidelines.

5.2 PHARMACOKINETIC PROPERTIES

Absorption and distribution

Following oral administration, candesartan cilexetil is converted to the active drug candesartan. The absolute bioavailability of candesartan is approximately 40% after an oral solution of candesartan cilexetil. The relative bioavailability of the tablet formulation compared with the same oral solution is approximately 34%, with little variability. The absolute bioavailability of candesartan following administration of the tablet is approximately 14%. The mean peak plasma concentration (C_{max}) is

reached 3-4 hours after taking a tablet. The candesartan plasma concentrations increase linearly with increasing doses in the therapeutic dose range.

The area under the plasma concentration versus time curve (AUC) of candesartan is not significantly affected by food. The peak concentration (C_{max}) is increased by 26% and the rate of absorption is increased when taken with food. These changes are unlikely to result in clinically significant effects.

Candesartan is highly bound to plasma protein (more than 99%). The apparent volume of distribution (V_{ss}) of candesartan is 0.1 L/kg.

Metabolism and excretion

Candesartan is mainly eliminated unchanged via urine and bile and is eliminated by hepatic metabolism only to a minor extent (CYP2C9). 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 ^{14}C -labelled candesartan cilexetil about 30% and 70% of the total radioactivity is recovered in the urine and faeces, respectively.

Pharmacokinetics in Special Populations

In the elderly (over 65 years) both C_{max} and AUC of candesartan are increased in comparison to young subjects. An initial dose of 8 mg is recommended (see section 4.2 DOSE AND METHOD OF ADMINISTRATION).

In patients with mild to moderate renal impairment C_{max} and AUC of candesartan increased during repeated dosing by approximately 50% and 70% respectively, but $t_{1/2}$ was not altered, compared to patients with normal renal function. The corresponding changes in patients with severe renal impairment were approximately 50% and 110% respectively. The terminal $t_{1/2}$ of candesartan was approximately doubled in patients with severe renal impairment. AUC of candesartan in patients undergoing haemodialysis was similar to that in patients with severe renal impairment.

In patients with mild to moderate hepatic impairment, there was a 23% increase in the AUC of candesartan. No initial dosage adjustment is necessary in these patients.

Pharmacokinetic Results of the Bioequivalence Study

A bioavailability study was conducted comparing the generic candesartan cilexetil 32 mg tablet with that of the originator. The generic and originator mean C_{max} for candesartan was 5.476 ng/mL and 5.530 ng/mL respectively. The C_{max} point estimate for candesartan was 94.75% with the 90% confidence interval between 87.80% and 102.37%. The AUC_{0-t} of the generic is 7.907 ng•hr/mL, and the mean AUC_{0-t} point estimate for candesartan was 90.98% with the 90% confidence interval between 86.34% and 95.87%. The T_{max} for the generic and originator tablets was 3.9 hours and 4.3 hours respectively.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Mutagenicity

Candesartan showed no evidence of genotoxic potential in a series of assay for gene mutations (*Salmonella typhimurium*, *Escherichia coli*, Mouse L5178Y cells and CHO cells), chromosomal aberrations (mouse nucleus assay) and unscheduled DNA synthesis. The active metabolite, candesartan, caused an increase in chromosomal aberrations *in vitro* (CHL cells) but not *in vivo* (mouse micronucleus assay).

Carcinogenicity

There was no evidence of carcinogenicity when candesartan cilexetil was orally administered to mice and rats for up to 104 weeks at doses up to 100 and 1000 mg/kg/day, respectively. Rats received the drug by gavage whereas mice received the drug by dietary administration. These (maximally tolerated) doses of candesartan cilexetil provided systematic exposures to candesartan (AUCs) that were, in mice, approximately 7 times and, in rats, more than 70 times the exposure in man at the maximum recommended daily human dose (32 mg).

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

In addition to candesartan cilexetil, ADESAN tablets also contain lactose monohydrate, carmellose calcium, glyceryl monostearate, hydroxypropylcellulose, iron oxide red CI77491, maize starch, magnesium stearate.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C in original container. Protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

Container type: Blister pack

Pack sizes: 7*, 28*, 30

*Some strengths, pack sizes and/or pack types may not be marketed.

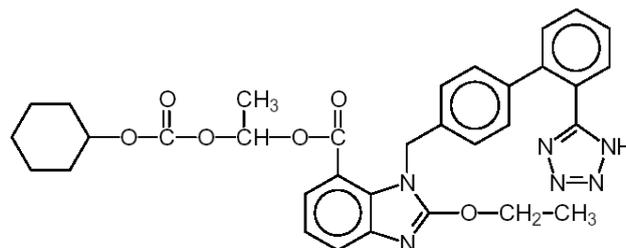
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Structure

Structural formula :



Molecular formula : C₃₃H₃₄N₆O₆

Molecular weight : 610.67

CAS Number

145040-37-5

Candesartan cilexetil a white to off white powder and is practically insoluble in water. Three polymorphic forms have been identified; crystal form I, crystal form II and an amorphous form. Crystalline form I is used in ADESAN.

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR**Alphapharm Pty Limited**

Level 1, 30 The Bond

30 – 34 Hickson Road

Millers Point NSW 2000

www.mylan.com.au

9 DATE OF FIRST APPROVAL

20/02/2013

10 DATE OF REVISION

4 December 2019

Summary Table of Changes

Section Changed	Summary of New Information
All	Reformat of the PI to align with updated Australian form for providing product information Minor editorial changes and IHIN updates

Adesan_pi\1019/01