# ATACAND®

Candesartan Cilexetil

**PRODUCT INFORMATION**

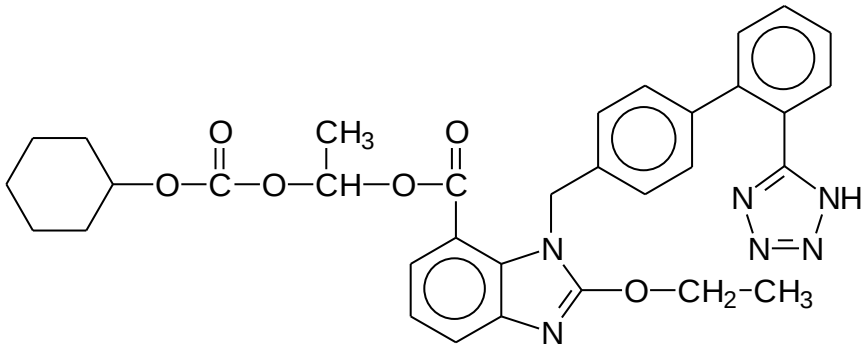
## NAME OF THE MEDICINE

The active ingredient in ATACAND® is candesartan cilexetil.

The CAS number is 145040-37-5. The molecular weight is 610.7.

The molecular formula is $C_{33}H_{34}N_6O_6$.

The chemical structure of candesartan cilexetil is



## DESCRIPTION

The chemical name for candesartan cilexetil is (±)-1-(cyclohexyloxycarbonyl-oxy) ethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl] methyl]-1H-benzimadozole-7-carboxylate.

It is 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 ATACAND.

ATACAND (candesartan cilexetil) is available in 4 mg, 8 mg, 16 mg and 32 mg tablets.

In addition to candesartan cilexetil, ATACAND also contains carmellose calcium, hyprolose, iron oxide - red (8 mg, 16 mg and 32 mg tablets only), lactose monohydrate, magnesium stearate, maize starch and macrogol 8000.

## PHARMACOLOGY

### Pharmacodynamics

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 ($AT_1$) receptor.

ATACAND 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 $AT_1$ 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 ATACAND. Candesartan does not bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

In hypertension, ATACAND 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.

ATACAND 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.

ATACAND 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 ATACAND.

ATACAND 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. ATACAND reduces urinary protein excretion in hypertensive patients with microalbuminuria or nephropathy of different aetiology. ATACAND 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 **PRECAUTIONS - Use in pregnancy, Use during lactation**).

## Pharmacokinetics

*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 serum concentration ($C_{max}$) is reached 3-4 hours after taking a tablet. The candesartan serum concentrations increase linearly with increasing doses in the therapeutic dose range. The area under the serum 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 elimination*

Candesartan is mainly eliminated unchanged via urine and bile and is eliminated by hepatic metabolism only to a minor extent. 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 **DOSAGE AND 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 was 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.

## 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).

| | **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

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).

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 ≤40%), ATACAND decreases systemic vascular resistance and pulmonary capillary wedge pressure, increases plasma renin activity and angiotensin II concentration, and decreases aldosterone levels.

Treatment with ATACAND 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) programme comprising 3 studies (CHARM-Alternative, CHARM-Added and CHARM-Preserved). In all 3 studies, patients on optimal baseline therapy were randomised to placebo or ATACAND (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 ≤40% not treated with an ACE inhibitor because of intolerance.

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 ≤40% treated with ACE inhibitors.

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.

| *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=0.118 | 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 ATACAND resulted in improved NYHA functional class in CHARM-Alternative and CHARM-Added (p=0.008 and p=0.020 respectively).

The beneficial effects of ATACAND on cardiovascular mortality and CHF hospitalisation were consistent irrespective of age, gender and concomitant medication. ATACAND 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.

## INDICATIONS

Treatment of hypertension.

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

## CONTRAINDICATIONS

Hypersensitivity to any component of ATACAND.

Pregnancy and lactation (see **PRECAUTIONS - Use in pregnancy**).

Severe hepatic impairment and/or cholestasis.

The use of ATACAND 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/1.73m$^2$).

## PRECAUTIONS

### 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, excessive blood pressure decrease in patients with ischaemic heart disease or atherosclerotic cerebrovascular disease could result in a myocardial infarction or stroke.

### Kidney transplantation

There is limited clinical experience regarding ATACAND use 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 ATACAND in these patients is not recommended.

### Hypotension

Hypotension may occur during treatment with ATACAND 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)

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 RAAS through the combined use of ATACAND with an ACE-inhibitor or aliskiren is therefore not recommended (see **INTERACTIONS WITH OTHER MEDICINES**).

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 ATACAND with aliskiren is contraindicated in patients with diabetes mellitus (type I or II) or moderate to severe renal impairment (GFR<60ml/min/1.73m$^2$) (see **CONTRAINDICATIONS**).

### Use in heart failure

Triple combination of ATACAND 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 ATACAND 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 ATACAND, hyperkalaemia may occur. During treatment with ATACAND 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.

### Renal impairment

As with other agents inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible patients treated with ATACAND. When ATACAND 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 $m^2$ BSA). Evaluation of patients with heart failure should include periodic assessments of renal function. During dose titration of ATACAND, monitoring of serum creatinine and potassium is recommended.

### Haemodialysis

During dialysis the blood pressure may be particularly sensitive to $AT_1$-receptor blockade as a result of reduced plasma volume and activation of the renin-angiotensin-aldosterone system. Therefore, ATACAND should be carefully titrated with thorough monitoring of blood pressure in patients on haemodialysis (see **DOSAGE AND ADMINISTRATION**).

### 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 ATACAND.

### 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.

### Carcinogenicity/mutagenicity

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).

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).

### 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 – Category D

The use of ATACAND is contraindicated during pregnancy (see **CONTRAINDICATIONS**). Patients receiving ATACAND 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 ATACAND 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, breast feeding should be discontinued if the use of ATACAND is considered essential.

### 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.

## INTERACTIONS WITH OTHER MEDICINES

### Dual blockade of the renin-angiotensin-aldosterone system (RAAS)

The combination of ATACAND with aliskiren-containing medicine is contraindicated in patients with diabetes mellitus (type I or II) or moderate to severe renal impairment (GFR<60ml/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 **CONTRAINDICATIONS** and **PRECAUTIONS**).

### 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. ethinyloestradiol/ 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.

ATACAND may be administered with other antihypertensive agents.

## ADVERSE EFFECTS

### Hypertension

ATACAND 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. ATACAND 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.

| | **Monotherapy Studies** | | **Combination Studies** | | |
|---|---|---|---|---|---|
| **Adverse Event** | **Placebo** | **ATACAND** | **Placebo** | **ATACAND** | **ATACAND + HCTZ** |
| | **(n=573)** | **(n=1388)** | **(n=205)** | **(n=444)** | **(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 |

| Adverse Event | Monotherapy Studies | | Combination Studies | | |
|---|---|---|---|---|---|
| | Placebo | ATACAND | Placebo | ATACAND | ATACAND + HCTZ |
| | (n=573) | (n=1388) | (n=205) | (n=444) | (n=673) |
| 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 effects of ATACAND 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 ATACAND. 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 ATACAND in heart failure patients was consistent with the pharmacology of the drug and the health status of the patients. In the CHARM clinical programme, comparing ATACAND 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 (≥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 **PRECAUTIONS**).

### 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 **PRECAUTIONS**).

Rare reports of rhabdomyolysis have been reported in patients receiving angiotension 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.

## DOSAGE AND ADMINISTRATION

ATACAND should be taken once daily with or without food.

### Paediatrics

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

### Hypertension

The recommended maintenance dose of ATACAND 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 ATACAND, combination with a thiazide diuretic is recommended.

### Geriatrics

An initial dose of 8 mg is recommended.

### Hepatic insufficiency

*Patients with hepatic impairment:* Dose titration is recommended in patients with mild to moderate chronic liver disease, and a lower initial dose of 4 mg should be considered.

ATACAND should not be used in patients with severe hepatic impairment and/or cholestasis (see **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/1.73m$^2$ BSA). In patients with severely impaired renal function (i.e. creatinine clearance <30 mL/min/1.73m$^2$ BSA) including patients on haemodialysis a lower initial dose of 4 mg should be considered.

### Heart failure

The usual recommended initial dose of ATACAND 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 **PRECAUTIONS**).

### Special patient populations

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

### Concomitant therapy

ATACAND can be administered with other heart failure treatment, including ACE inhibitors, beta-blockers, diuretics and digitalis or a combination of these medicines (see **PRECAUTIONS** and **PHARMACOLOGY - Pharmacodynamics**).

## OVERDOSAGE

### 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. Contact the Poisons Information Centre for advice on management.

## PRESENTATION AND STORAGE CONDITIONS

**ATACAND® 4 mg tablets** are round (diameter 7 mm), white tablets with a score and marked “A/CF” on one side and 004 on the other side, in blister packs of 7 and 30 tablets.

**ATACAND® 8 mg tablets** are round (diameter 7 mm), light pink tablets with a score and marked “A/CG” on one side and marked 008 on the other side, in blister packs of 7 and 30 tablets.

**ATACAND® 16 mg tablets** are round (diameter 7 mm), pink tablets with a score and marked “A/CH” on one side and marked 016 on the other side, in blister packs of 7, and 30 tablets. A 28 tablet pack size is registered for ATACAND® 4, 8 and 16 mg tablets but not marketed.

**ATACAND® 32 mg tablets** are round, pink, biconvex tablets, with a score and marked “A/CL” on one side and marked 032 on the other side, in blister packs of 7 and 30 tablets.

### Storage

3 years if stored below 30°C.

## NAME AND ADDRESS OF THE SPONSOR

AstraZeneca Pty Ltd
ABN 54 009 682 311
66 Talavera Road
MACQUARIE PARK NSW 2113

Telephone: 1800 805 342

## POISON SCHEDULE OF THE MEDICINE

Schedule 4 (Prescription only medicine)

## DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

29 July 1998

## DATE OF MOST RECENT AMENDMENT

10 January 2018