NEW ZEALAND DATA SHEET

1. PRODUCT NAME

ATACAND® 4 mg Tablets
ATACAND® 8 mg Tablets
ATACAND® 16 mg Tablets
ATACAND® 32 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains candesartan cilexetil 4 mg, 8 mg, 16 mg or 32 mg.

Excipient with known effect:
4 mg: Each tablet contains 93.4 mg lactose monohydrate.
8 mg: Each tablet contains 89.4 mg lactose monohydrate.
16 mg: Each tablet contains 81.4 mg lactose monohydrate.
32 mg: Each tablet contains 162.8 mg lactose monohydrate.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets

ATACAND 4 mg are round (diameter 7 mm), white tablets with a score and marked A/CF on one side and 004 on the other side.

ATACAND 8 mg 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.

ATACAND 16 mg are round (diameter 7 mm), pink tablets with a score and marked A/CH on one side and marked 016 on the other side.

ATACAND 32 mg are round (diameter 9.5 mm), pink tablets with a score and marked A/CL on one side and 032 on the other side.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Hypertension.

Treatment of patients with heart failure and left ventricular systolic dysfunction. Treatment with ATACAND reduces mortality, reduces hospitalisation due to heart failure and improves symptoms.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage in Hypertension

The recommended initial and maintenance dose of ATACAND is 8 mg once daily. The dose may be increased to 16 mg once daily. In patients who require further blood pressure reduction, the dose may be increased to 32 mg once daily.

Therapy should be adjusted according to blood pressure response. The maximal antihypertensive effect is attained within 4 weeks after initiation of treatment.

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

Use in the elderly

No initial dosage adjustment is necessary for elderly patients.

Use in impaired renal function

No initial dosage adjustment is necessary in patients with mild to moderate impaired renal function (i.e. creatinine clearance ≥30-80 mL/min/1.73 m^2 BSA). In patients with severe impaired renal function (i.e. creatinine clearance <30 mL/ min/1.73 m^2 BSA), including patients on haemodialysis a lower initial dose of 4 mg should be considered.

Use in impaired hepatic function

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 section 4.3).

Concomitant therapy

ATACAND may be administered with other antihypertensive agents (see section 5.1).

Dosage in Heart Failure

The usual recommended initial dose for ATACAND is 4 mg once daily. Up-titration to the target dose of 32 mg once daily or the highest tolerated dose is done by doubling the dose at intervals of at least 2 weeks (see section 4.4).

Special patient populations

No initial dose adjustment is necessary for elderly patients.

Concomitant therapy

ATACAND can be administered with other heart failure treatment, including ACE inhibitors, beta-blockers, diuretics and digitalis or a combination of these medicinal products (see sections 4.4 and 5.2).

Administration

ATACAND should be taken once daily with or without food.

Use in children

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

4.3 CONTRAINDICATIONS

- Hypersensitivity to any component of ATACAND.
- Pregnancy and lactation.
- Severe hepatic impairment and/or cholestasis.
- The use of candesartan cilexetil 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).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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 hypovolaemia 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 section 4.5).

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 candesartan cilexetil 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 section 4.3).

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.

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.

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.

Kidney transplantation

There is limited clinical evidence regarding ATACAND use in patients who have undergone renal transplant.

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 section 4.2).

Hepatic impairment

There is only limited experience in patients with severe hepatic impairment and/or cholestasis.

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.

Hyperkalaemia

Based on experience with the use of other drugs that affect the renin-angiotensin-aldosterone system, concomitant use of potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium or other drugs that may increase potassium levels (e.g. heparin, cotrimoxazole) 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.

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. Very rarely, hypotension may be severe such that it may warrant the use of intravenous fluids and/or vasopressors.

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.

4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION

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 sections 4.3 and 4.4).

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

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.

The antihypertensive effect of angiotensin II receptor antagonists, including ATACAND may be attenuated by NSAIDs; including selective 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.

The antihypertensive effect of ATACAND may be enhanced by other antihypertensives.

The bioavailability of candesartan is not affected by food.

4.6 FERTILITY, PREGNANCY AND LACTATION

Pregnancy

The use of ATACAND is contraindicated during pregnancy (see section 4.3). 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.

When used in pregnancy, medicines that act directly on the renin-angiotensin system can cause foetal and neonatal injury and death. 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) (see section 5.3).

Breast-feeding

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 (see section 4.3).

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effect of ATACAND on the ability to drive and use machines has not been studied, but based on its pharmacodynamic properties ATACAND is unlikely to affect this ability. When driving vehicles or operating machines, it should be taken into account that dizziness or weariness may occur during treatment.

4.8 UNDESIRABLE EFFECTS

Treatment of hypertension

ATACAND was well tolerated in controlled clinical studies showing an adverse event profile comparable to that of placebo. Generally adverse events were mild and transient.

The overall incidence of adverse events 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%).

Laboratory findings

In general, there were no clinically important influences 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. Increases in S-ALAT (S-GPT) were reported as adverse events slightly more often with ATACAND than with placebo (1.3% vs 0.5%). No routine monitoring of laboratory variables is necessary for patients receiving ATACAND. However, in patients with severe renal impairment, periodic monitoring of serum potassium and creatinine levels should be considered.

Treatment of 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 section 4.4).

Post Marketing

The following adverse reactions have been reported very rarely (<1/10,000) in post marketing experience:

Blood and lymphatic system disorders:
Leukopenia, neutropenia and agranulocytosis

Metabolism and nutrition disorders:
Hyperkalaemia, hyponatraemia

Nervous system disorders:
Dizziness

Respiratory, thoracic and mediastinal disorders:
Cough

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

Renal and urinary disorders:
Renal impairment, including renal failure in susceptible patients (see section 4.4).

Although causality to candesartan has not been established, palpitation has been very rarely reported as an adverse event during post-marketing surveillance

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

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 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. Sympathomimetic drugs may be administered if the above-mentioned measures are not sufficient.

Candesartan cannot be removed by haemodialysis.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764 766).

5.1 PHARMACOLOGICAL PROPERTIES

5.2 PHARMACODYNAMIC PROPERTIES

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 ACE, which converts angiotensin I to angiotensin II and degrades bradykinin. Since there is no effect on the degradation of bradykinin, angiotensin II receptor antagonists are unlikely to be associated with cough. In controlled clinical studies comparing ATACAND with ACE inhibitors, the incidence of cough was lower in patients receiving ATACAND.

Candesartan does not bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation. The antagonism of the angiotensin II (AT_1) receptors results in dose related increases in plasma renin activity, angiotensin I and angiotensin II concentrations and a decrease in plasma aldosterone concentration.

CLINICAL EFFICACY AND SAFETY

Hypertension

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.

After administration of a single dose of ATACAND onset of antihypertensive effect generally occurs within 2 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.

ATACAND once daily provides effective and smooth blood pressure reduction over 24 hours, with little difference between maximum and trough effects during the dosing interval. In two 8-week randomised, double-blind studies, the blood pressure lowering effects of ATACAND and losartan were evaluated in a total of 1,268 patients with mild to moderate hypertension. In both studies, the reduction of systolic and diastolic blood pressure was significantly greater with ATACAND (32 mg once daily). In a pooled analysis, the trough blood pressure reduction (systolic/diastolic) was 13.1/10.5 mmHg with ATACAND and 10.0/8.7 mmHg with losartan potassium (100 mg once daily). The mean difference in blood pressure reduction was 3.1/1.8 mmHg ($p<0.0001/p<0.0001$).

ATACAND can be used as monotherapy or in combination with other antihypertensive drugs, such as thiazide diuretics, dihydropyridine calcium antagonists and lisinopril, for enhanced efficacy.

ATACAND is similarly effective in patients irrespective of age and gender. ATACAND is effective in reducing blood pressure regardless of race, although the effect is somewhat less in black patients (usually a low-renin population). This is generally true for drugs that block the renin-angiotensin-aldosterone system.

ATACAND increases renal blood flow and either has no effect on or increases glomerular filtration rate while renal vascular resistance and filtration fraction are reduced. ATACAND also reduces urinary albumin excretion in patients with type II diabetes mellitus, hypertension and microalbuminuria. In hypertensive patients with type II diabetes mellitus, 12 weeks treatment with ATACAND 8 mg to 16 mg had no adverse effects on blood glucose or lipid profile.

In the SCOPE (Study on Cognition and Prognosis in the Elderly) trial, the effects of candesartan cilexetil based antihypertensive treatment on cardiovascular morbidity and mortality, cognitive function and quality of life were assessed in 4,937 elderly patients (aged 70-89 years) with hypertension (SBP 160-179 mmHg and/or DBP 90-99 mmHg). The table shows the study results for the primary endpoint (major cardiovascular events) and its components. Both treatment regimens lowered systolic and diastolic blood pressure effectively and were generally well tolerated. Cognitive function and quality of life were well maintained in both treatment arms.

	Candesartan cilexetil* Number of patients with a first event (N=2477)	**Control* Number of patients with a first event (N=2460)**	**Relative risk (95% CI)**	**P-value**
Major CV events	242	268	0.89 (0.75-1.06)	0.19
- CV mortality	145	152	0.95 (0.75-1.19)	0.63
- Non-fatal stroke	68	93	0.72 (0.53-0.99)	0.04
- Non-fatal MI	54	47	1.14 (0.77-1.68)	0.52

*Any previous antihypertensive treatment was standardized to hydrochlorothiazide 12.5 mg once daily before randomisation. Other antihypertensive treatment was added to the double-blind study medication

(candesartan cilexetil 8-16 mg or corresponding placebo once daily) if SBP remained ≥ 160 mmHg and/or DBP ≥ 90 mmHg.

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. This multinational, placebo controlled, double-blind study programme in CHF patients with NYHA functional class II to IV consisted of three separate studies: CHARM-Alternative (n=2,028) in patients with LVEF ≤40% not treated with an ACE inhibitor because of intolerance, CHARM-Added (n=2,548) in patients with LVEF ≤40% and treated with an ACE inhibitor, and CHARM-Preserved (n=3,023) in patients with LVEF >40%. 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.

The composite endpoint of cardiovascular mortality or first CHF hospitalisation was significantly reduced with ATACAND in comparison with placebo in CHARM-Alternative (hazard ratio (HR) 0.77, 95% CI 0.67-0.89, p<0.001) and in CHARM-Added (HR 0.85, 95% CI 0.75-0.96, p=0.011). This corresponds to a relative risk reduction of 23% and 15% respectively. A reduction, although statistically non-significant, was also achieved in CHARM-Preserved (HR 0.89, 95% CI 0.77-1.03, p=0.118).

The composite endpoint of all-cause mortality or first CHF hospitalisation was also significantly reduced with ATACAND in CHARM-Alternative (HR 0.80, 95% CI 0.70-0.92, p=0.001) and CHARM-Added (HR 0.87, 95% CI 0.78-0.98, p=0.021), and a similar trend was observed in CHARM-Preserved (HR 0.92, 95% CI 0.80-1.05, p=0.221).

Both the mortality and morbidity (CHF hospitalisation) components of the composite endpoints contributed to the favourable effects of ATACAND in CHARM-Alternative and CHARM-Added. The favourable effects indicated in CHARM-Preserved were due to reduced CHF hospitalisation.

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).

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.

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 very little variability. The mean peak serum concentration (C_{max}) is reached 3 to 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%). The apparent volume of distribution of candesartan is 0.1 L/kg.

Metabolism and elimination

Candesartan is mainly eliminated unchanged via urine and bile and only eliminated by hepatic metabolism (CYP2C9) to a minor extent. Available interaction studies indicate no effect on CYP2C9 and CYP3A4. Based on *in vitro* data, no interaction would be expected to occur *in vivo* with drugs whose metabolism is dependent upon cytochrome P450 isoenzymes CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1 OR CYP3A4. 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 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.

Pharmacokinetics in special populations

In the elderly (over 65 years) both C_{max} and AUC of candesartan are increased, by approximately 50% and 80% respectively, in comparison to young subjects. However, the blood pressure response and the incidence of adverse events are similar after a given dose of ATACAND in young and elderly patients.

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 $t_{½}$ 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 $t_{½}$ of candesartan was approximately doubled in patients with severe renal impairment. The AUC of candesartan in patients undergoing haemodialysis was similar to that in patients with severe renal impairment (see section 4.2).

In patients with mild to moderate hepatic impairment, there was an increase in the AUC of candesartan of approximately 20%. In patients with moderate to severe hepatic impairment, the increase in the AUC of candesartan was approximately 80%.

There is only limited experience in patients with severe hepatic impairment and/or cholestasis (see section 4.2).

5.3 PRECLINICAL SAFETY DATA

In a variety of preclinical safety studies conducted in several species, expected exaggerated pharmacological effects, 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. Animal studies with candesartan cilexetil have demonstrated late foetal and neonatal injury in the kidney. The mechanism is believed to be pharmacologically mediated through effects on the renin-angiotensin-aldosterone system.

There was no evidence of mutagenicity, clastogenicity or carcinogenicity.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Calcium carboxymethylcellulose, hydroxypropyl cellulose, iron oxide E 172 (only 8 mg, 16 mg and 32 mg tablets), lactose, magnesium stearate, maize starch and polyethylene glycol.

6.2 INCOMPATIBILITIES

Nil

6.3 SHELF-LIFE

3 years in PVC/PVDC blisters

6.4 SPECIAL PRECAUTION FOR STORAGE

Store below 30 °C.

6.5 NATURE AND CONTENTS OF CONTAINER

PVC/PVDC blisters - Press through packages of thermoformed PVC/PVDC with an aluminium foil as enclosure web.

4 mg tablet: Blister packs of 30 tablets
8 mg tablet: Blister packs of 30 tablets
16 mg tablet: Blister packs of 30 tablets
32 mg tablet: Blister packs of 30 tablets

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Return unused and expired medicines to your local pharmacy for disposal.

7. MEDICINES SCHEDULE

Prescription Medicine

8. SPONSOR

AstraZeneca Limited
PO Box 87453
Meadowbank
Auckland 1742.
Telephone: (09) 306 5650

9. DATE OF FIRST APPROVAL

ATACAND 4, 8 and 16 mg: 14 May 1998
ATACAND 32 mg: 25 May 2006

10. DATE OF REVISION OF THE TEXT

5 February 2020

CDS 210515

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
8	Postal address amended.