SCHEDULING STATUS

S3

1 NAME OF MEDICINE

ATACAND® 8 mg tablets

ATACAND® 16 mg tablets

ATACAND® 32 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

ATACAND 8 mg: Each tablet contains 8 mg candesartan cilexetil.

ATACAND 16 mg: Each tablet contains 16 mg candesartan cilexetil.

ATACAND 32 mg: Each tablet contains 32 mg candesartan cilexetil.

Contains sugar (lactose monohydrate).

ATACAND 8 mg: Each tablet contains 89,4 mg lactose monohydrate.

ATACAND 16 mg: Each tablet contains 80,7 mg lactose monohydrate.

ATACAND 32 mg: Each tablet contains 161,5 mg lactose monohydrate.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablets.

ATACAND 8 mg:

A light pink, circular, biconvex tablet with a score and engraved *A/CG* on one side and 008 on the other side.

ATACAND 16 mg:

A pink, circular, biconvex tablet with a score and engraved *A/CH* on one side and 016 on the other side.

ATACAND 32 mg:

A pink, circular, biconvex tablet with a score and engraved *A/CL* on one side and 032 on the other side.

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

ATACAND is indicated for mild to moderate hypertension.

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

Heart failure

Treatment with ATACAND reduces mortality, reduces hospitalisation due to heart failure, and improves symptoms in patients with left ventricular systolic dysfunction (LVEF ≤ 40 %).

4.2 Posology and method of administration

Dosage in hypertension

The recommended initial dose of ATACAND is 8 mg once daily. The usual maintenance dose is 8 mg to 16 mg once daily.

The maximal antihypertensive effect is attained within 4 weeks of initiation of treatment.

Some patients may receive an additional benefit by increasing the dose to 32 mg once daily.

Use in elderly

No initial dosage adjustment is necessary for elderly patients with normal renal and hepatic function.

Use in impaired renal function

No initial dosage adjustment is necessary in patients with mild to moderate renal impairment (i.e. creatinine clearance ≥ 30 mL/min/1,73m^2 BSA). In patients with more severe renal impairment (i.e. creatinine clearance < 15 – 30 mL /min/1,73 m^2 BSA), the clinical experience is limited, and a lower initial dose of 4 mg should be used.

Use in impaired hepatic function

No initial dosage adjustment is necessary in patients with mild to moderate hepatic impairment. There is no experience available in patients with severe hepatic impairment and/or cholestasis (see section 4.3).

Concomitant therapy

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

Use in black patients

The antihypertensive effect of ATACAND is less in black than non-black (Caucasian, Asian and other) patients. Consequently, up-titration of ATACAND and concomitant therapy (such as thiazide diuretics) may be more frequently needed for blood pressure control in black than non-black patients.

Dosage in 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 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 or in patients with renal or mild to moderate 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 section 5.1).

Paediatric population

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

Method of administration

For oral use.

ATACAND should be taken once daily with or without food.

4.3 Contraindications

- Hypersensitivity to candesartan cilexetil or to any of the excipients listed in section 6.1.
- Severe renal function impairment (creatinine clearance < 30 mL/min) (see section 4.4).
- Second and third trimester of pregnancy and lactation (see sections 4.4 and 4.6).
- Severely impaired hepatic function and/or cholestasis.
- Bilateral renal artery stenosis.
- Renal artery stenosis in patients with a single kidney.
- Aortic valve stenosis.
- A history of angioedema related to previous therapy with ACE inhibitors or angiotensin receptor blockers (ARB's). These patients must never again be given these medicines.
- Hereditary or idiopathic angioedema.
- Hypertrophic Obstructive Cardiomyopathy (HOCM).
- Concomitant therapy with potassium sparing diuretics such as spironolactone, triamterene, amiloride (see section 4.5).

- Porphyria.
- Lithium therapy: concomitant administration with ATACAND may lead to toxic blood concentrations of lithium (see section 4.5).
- Children aged below 1 year (see section 5.3)
- The concomitant use with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 mL/min/1,73m^2) (see sections 4.4 and 4.5).
- Concomitant use of fluoroquinolones with ACE inhibitors/Renin-Angiotensin blockers is contraindicated in patients with moderate to severe renal impairment.

4.4 Special warnings and precautions for use

Should a women become pregnant while receiving ATACAND, the treatment should be stopped promptly and switched to a different class of antihypertensive medicine (see sections 4.3 and 4.6).

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

There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers (ARBs) or aliskiren may increase the risk of hypotension, hyperkalaemia and decreases renal function (including renal failure). Dual blockade of RAAS through combined use of ATACAND and aliskiren is therefore contraindicated (see section 4.3).

ATACAND should not be used concomitantly with aliskiren (see section 4.3).

ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

Intestinal angioedema

Intestinal angioedema has been reported in patients treated with angiotensin II receptor antagonists, including candesartan, the active ingredient of Atacand (see section 4.8). These patients presented with abdominal pain, nausea, vomiting and diarrhoea. Symptoms resolved after discontinuation of angiotensin II receptor antagonists.

If intestinal angioedema is diagnosed, candesartan, the active ingredient of Atacand, should be discontinued and appropriate monitoring should be initiated until complete resolution of symptoms has occurred.

Renal impairment

Concomitant use of fluoroquinolones and ACE inhibitors/renin-angiotensin receptor blockers may precipitate acute kidney injury (AKI), especially those with moderate to severe renal impairment and elderly patients (see section 4.3). Renal function should be assessed before initiating treatment, and monitored during treatment, with fluoroquinolones or ACE inhibitors/renin-angiotensin receptor blockers.

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 (creatinine clearance < 15 mL/min/1,73 m^2 BSA). In these patients, ATACAND should be carefully titrated with thorough monitoring of blood

pressure.

Evaluation of patients with heart failure should include periodic assessments of renal function, especially in elderly patients 75 years or older, and patients with impaired renal function. During dose titration of ATACAND, monitoring of serum creatinine and potassium is recommended. Clinical trials in heart failure did not include patients with serum creatinine > 265 μ mol/L (> 3 mg/dL).

Concomitant therapy with an ACE inhibitor in heart failure

The risk of adverse reactions, especially hypotension, hyperkalaemia and decreased renal function (including acute renal failure), may increase when ATACAND is used in combination with an ACE-inhibitor. Triple combination of an ACE-inhibitor, a mineralocorticoid receptor antagonist and ATACAND 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.

ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

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.

Kidney transplantation

There is no experience regarding the administration of ATACAND in patients with recent kidney transplantation.

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.

Anaesthesia and surgery

Hypotension may occur during anaesthesia and surgery in patients treated with ATACAND 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.

Primary hyperaldosteronism

Patients with primary hyperaldosteronism will not generally respond to antihypertensive medicines acting through inhibition of the renin-angiotensin-aldosterone system. Therefore, the use of ATACAND is not recommended.

Hyperkalaemia

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.

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.

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 medicines that affect this system has been associated with acute hypotension, azotaemia, oliguria or, rarely, acute renal failure. Excessive blood pressure decreases in patients with ischaemic cardiopathy or ischaemic cerebrovascular disease could result in a myocardial infarction or stroke.

The antihypertensive effect of ATACAND may be enhanced by other medicines with blood pressure lowering properties, whether prescribed as an antihypertensive or prescribed for other indications.

Paediatric population

Use in paediatric patients including patients with renal impairment

ATACAND has not been studied in children with a glomerular filtration rate less than 30 mL/min/1,73m^2 (see section 4.2).

For children with possible intravascular volume depletion (e.g. patients treated with diuretics, particularly those with impaired renal function), ATACAND treatment should be initiated under close medical supervision and a lower starting dose should be considered (see section 4.2).

In post-menarche patients the possibility of pregnancy should be evaluated on a regular basis. Appropriate information should be given and/or action taken to prevent the risk of exposure during pregnancy (see sections 4.3 and 4.6).

ATACAND contains lactose monohydrate

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take ATACAND.

4.5 Interaction with other medicines and other forms of interaction

Dual blockade of the RAAS with ARBs, ACE inhibitors, or aliskiren

Clinical trial data has shown that dual blockade of the renin-angiotensin-aldosterone-system (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 (see sections 4.3 & 4.4).

Concomitant use of fluoroquinolones and ACE inhibitors/renin-angiotensin receptor blockers may precipitate acute kidney injury (AKI) (see sections 4.3 & 4.4).

Concomitant use of potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium, or other medicines (e.g. heparin) may increase potassium levels. Monitoring of potassium should be undertaken as appropriate (see sections 4.3 & 4.4).

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). Use of candesartan with lithium is not recommended (see section 4.3). If the combination proves necessary, careful monitoring of serum lithium levels is recommended.

When AIIRAs are administered simultaneously with non-steroidal anti-inflammatory drugs (NSAIDs) (i.e. selective COX-2 inhibitors, acetylsalicylic acid (> 3 g/day) and non-selective NSAIDs), attenuation of the antihypertensive effect may occur.

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 the elderly. Patients should be adequately hydrated, and consideration should be given to monitoring renal function after initiation of concomitant therapy, and periodically thereafter.

4.6 Fertility, pregnancy and lactation

Pregnancy

The use of ATACAND is not recommended during the first trimester of pregnancy (see section 4.4). The use of ATACAND is contraindicated during the second and third trimesters of pregnancy (see sections 4.3 and 4.4).

When used in pregnancy during the second and third trimesters, medicines that act directly on the renin-angiotensin system can cause foetal and neonatal injury and death. These medicines pass through the placenta and can be presumed to cause disturbance in foetal blood pressure regulatory mechanisms. Oligohydramnios as well as hypotension, oliguria and anuria in newborns, have been reported after administration in the second and third trimester. Cases of defective skull ossification have been observed. Premature and low birth mass can occur. Should exposure to AIIRAs have occurred from the second trimester of pregnancy, an ultrasound check of renal function and the skull is recommended.

Should a woman become pregnant while receiving ATACAND, the treatment must be stopped promptly and switched to a different medicine. Should a woman contemplate pregnancy, the doctor should institute alternative medication.

Safety in pregnancy and lactation has not been established (see section 4.3). When pregnancy is planned or confirmed, ATACAND should be discontinued.

Medicines affecting the renin-angiotensin system, such as ATACAND, can cause embryonal toxicity, foetal and neonatal morbidity and mortality when administered to pregnant women.

Women of childbearing age should ensure effective contraception.

ATACAND is contraindicated in pregnancy (see section 4.3).

Infants whose mother have taken AIIRAs should be closely observed for hypotension (see section 4.3 and 4.4).

Breastfeeding

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 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. 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

In controlled clinical studies, adverse reactions 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 %). In a pooled analysis of clinical trial data, the following common (> 1/100) adverse reactions with

candesartan cilexetil were reported based on an incidence of adverse events with candesartan cilexetil at least 1 % higher than the incidence seen with placebo. By this definition, the most commonly reported adverse reactions were dizziness/vertigo, headache and respiratory infection.

The table below presents adverse reactions from clinical trials and post-marketing experience. The frequencies used in the tables throughout this section are:

- Very common (≥ 1/10)
- Common (≥ 1/100 to < 1/10)
- Uncommon (≥ 1/1 000 to <1/100)
- Rare (≥ 1/10 000 to < 1/1 000)
- Very rare (<1/10 000)
- Not known (cannot be estimated from the available data).

System Organ Class	**Frequency**	**Undesirable Effect**
Infections and infestations	Common	Respiratory infection
Blood and lymphatic system disorders	Very rare	Leukopenia, neutropenia and agranulocytosis
Metabolism and nutrition disorders	Very rare	Hyperkalaemia, hyponatraemia
Nervous system disorders	Common	Dizziness/vertigo, headache
Respiratory, thoracic and mediastinal disorders	Very rare	Cough
Gastrointestinal disorders	Very rare	Nausea, intestinal angioedema
	Not known	Diarrhoea
Hepato-biliary disorders	Very rare	Increased liver enzymes, abnormal hepatic function or hepatitis
Skin and subcutaneous tissue disorders	Very rare	Angioedema, rash, urticaria, pruritus

Musculoskeletal and connective tissue disorders	Very rare	Back pain, arthralgia, myalgia
Renal and urinary disorders	Very rare	Renal impairment, including renal failure in susceptible patients (see section 4.4)

Laboratory findings

Small decreases in haemoglobin have been seen. Significant increases in creatinine, urea or potassium and decrease in sodium have been observed. In patients with severe renal impairment, periodic monitoring of serum potassium and creatinine levels should be considered.

Paediatric population

The safety of candesartan cilexetil was monitored in 255 hypertensive children and adolescents, aged 6 to < 18 years old, during a 4-week clinical efficacy study and a 1-year open label study (see section 5.1). In nearly all different system organ classes, the frequency of adverse events in children are within common/uncommon range. Whilst the nature and severity of the adverse events are similar to those in adults (see the table above), the frequency of all adverse events are higher in children and adolescent, particularly in:

- Headache, dizziness and upper respiratory tract infection, are “very common” (i.e. ≥ 1/10) in children and common (≥ 1/100 to <1/10) in adults.
- Cough is “very common” (i.e. >1/10) in children and very rare (<1/10 000) in adults.
- Rash is “common” (i.e. ≥ 1/100 to < 1/10) in children and “very rare” (<1/10 000) in adults.
- Hyperkalaemia, hyponatraemia and abnormal liver function are uncommon (≥ 1/1 000 to < 1/100) in children and very rare (< 1/10 000) in adults.
- Sinus arrhythmia, nasopharyngitis, pyrexia is “common” (i.e. ≥ 1/100 to < 1/10) and oropharyngeal pain is “very common” (i.e. ≥ 1/10) in children, but none are reported in adults. However, these are temporary and widespread childhood
- illnesses

The overall safety profile for ATACAND in paediatric patients does not differ significantly from the safety profile in adults.

Treatment of heart failure

The adverse experience profile of ATACAND in heart failure patients was consistent with the pharmacology of the medicine 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. The most commonly reported adverse reactions were hyperkalaemia, hypotension and renal impairment. These events were more common in patients over 70 years of age, diabetics, or subjects who received other medicines which affect the renin-angiotensin-aldosterone system, in particular an ACE inhibitor and/or spironolactone.

The table below presents adverse reactions from clinical trials and post-marketing experience.

System Organ Class	**Frequency**	**Undesirable Effect**
Blood and lymphatic system disorders:	Very rare	Leukopenia, neutropenia and agranulocytosis
Metabolism and nutrition disorders	Common	Hyperkalaemia
	Very rare	Hyponatraemia
Nervous system disorders	Very rare	Dizziness, headache
Vascular disorders	Common	Hypotension
Gastrointestinal disorders	Very rare	Nausea
Hepato-biliary disorders	Very rare	Increased liver enzymes, abnormal hepatic function or hepatitis
Skin and subcutaneous tissue disorders	Very rare	Angioedema, rash, urticaria, pruritus
Musculoskeletal and connective tissue disorders	Very rare	Back pain, arthralgia, myalgia

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

Laboratory findings

Hyperkalaemia and renal impairment are common in patients treated with ATACAND for the indication of heart failure. Increases in creatinine, urea and potassium. Periodic monitoring of serum creatinine and potassium is recommended (see section 4.4).

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 ATACAND. Healthcare providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safey APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on the SAHPRA website.

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

Candesartan is not removed by haemodialysis.

5 PHARMACOLOGICAL PROPERTIES

Category and class: A 7.1.3 Other hypotensives

Pharmacotherapeutic group: Angiotensin II antagonists, plain, ATC code: C09CA06.

5.1 Pharmacodynamic properties

Mechanism of action

Angiotensin II is the primary vasoactive hormone of the renin-angiotensin-aldosterone system and plays a role in the pathophysiology of hypertension, heart failure and other cardiovascular disorders. It also has a 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.

Pharmacodynamic effects

Candesartan cilexetil is a prodrug. After oral administration it is converted to the active drug, candesartan, by ester hydrolysis during absorption from the gastrointestinal tract. Candesartan is an angiotensin II receptor antagonist (AIIRA), selective for AT1 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. There is no effect on ACE and no potentiation of bradykinin or substance P. In controlled clinical trials comparing candesartan with ACE inhibitors, the incidence of cough was lower in patients receiving candesartan cilexetil. 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 (AT1) 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-related sustained reduction in arterial blood pressure over the dosage interval. 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 serous 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 begins within 2 hours. With continuous treatment, the maximum reduction in blood pressure is generally attained within 4 weeks and is sustained during long-term treatment. According to a meta-analysis, the average additional effect of a dose increase from 16 mg to 32 mg once daily was small. Taking into account the inter-individual variability, a more than average effect can be expected in some patients. 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.

Candesartan has a peak to trough ratio of peak versus trough effects of close to 1.

When ATACAND is used together with hydrochlorothiazide, the reduction in blood pressure is additive. An increased antihypertensive effect is also seen when ATACAND is combined with amlodipine or felodipine. Medicines that block the renin-angiotensin-aldosterone system have less pronounced antihypertensive effect in black patients (usually a low-renin population) than in non-black patients.

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. In a 3-month clinical study in hypertensive patients with type 2 diabetes mellitus and microalbuminuria, antihypertensive treatment with candesartan cilexetil reduced urinary albumin excretion (albumin/creatinine ratio, mean 30 %, 95 % CI 15 – 42 %). There are currently no data on the effect of candesartan on the progression to diabetic nephropathy.

Paediatric population – hypertension

The antihypertensive effects of candesartan were evaluated in hypertensive children aged 1 to < 6 years and 6 to < 17 years in two randomised, double-blind multicentre, 4-week dose ranging studies.

In children aged 6 to < 17 years there was a trend for a lesser effect on blood pressure in black patients compared to non-black patients.

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 due to cardiovascular events and hospitalisation due to CHF in patients with a left ventricular ejection fraction (LVEF) of ≤ 40 % and improves symptoms in these patients as shown in the Candesartan in Heart failure – Assessment of Reduction in Mortality and morbidity (CHARM) programme.

There was no benefit of ATACAND in patients with a LVEF of more than 40 %.

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

Two large randomised, controlled trials (ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) and VA NEPHRON-D (The Veterans Affairs Nephropathy in Diabetes)) have examined the use of the combination of an ACE inhibitor with an angiotensin II receptor blocker.

ONTARGET was a study conducted in patients with a history of cardiovascular or cerebrovascular disease, or type 2 diabetes mellitus accompanied by evidence of end-organ damage. VA NEPHRON-D was a study in patients with type 2 diabetes mellitus and diabetic nephropathy.

These studies have shown no significant beneficial effect on renal and/or

cardiovascular outcomes and mortality, while an increased risk of hyperkalaemia, acute kidney injury and/or hypotension as compared to monotherapy was observed. Given their similar pharmacodynamic properties, these results are also relevant for

other ACE-inhibitors and angiotensin II receptor blockers.

ACE-inhibitors and angiotensin II receptor blockers should therefore not be used concomitantly in patients with diabetic nephropathy.

ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints) was a study designed to test the benefit of adding aliskiren to a standard therapy of an ACE-inhibitor or an angiotensin II receptor blocker in patients with type 2 diabetes mellitus and chronic kidney disease, cardiovascular disease, or both. The study was terminated early because of an increased risk of adverse outcomes. Cardiovascular death and stroke were both numerically more frequent in the aliskiren group than in the placebo group and adverse events and serious adverse events of interest (hyperkalaemia, hypotension and renal dysfunction) were more frequently reported in the aliskiren group than in the placebo group.

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.

Candesartan cilexetil had an additional blood pressure lowering effect when added to hydrochlorothiazide.

5.2 Pharmacokinetic properties

Absorption and distribution

Following oral administration, candesartan cilexetil is converted to the active drug, candesartan. The mean peak serum concentration (C_{max}) is reached 3 to 4 hours following tablet intake. The candesartan serum concentration increases 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 litres/kg.

The bioavailability of candesartan is not affected by food.

Biotransformation and elimination

Candesartan is mainly eliminated unchanged via urine and bile and only to a minor extent eliminated by hepatic metabolism (CYP2C9). 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 medicines 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.

The total plasma clearance of candesartan is about 0,37 mL/min/kg, with renal clearance of about 0,19 mL /min/kg. 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 adults. However, the blood pressure response and the incidence of adverse events are similar after a given dose of candesartan cilexetil in young and elderly patients (see section 4.2).

In patients with mild (creatinine clearance 60 – 90 mL /min) and moderate (creatinine clearance 30 – 60 mL /min) renal impairment, C_{max} and AUC of candesartan increased during repeating 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 (creatinine clearance 15 – 30 mL /min) renal impairment were

approximately 50 % and 110 %, respectively. The terminal $t_{1/2}$ of candesartan was approximately doubled in patients with severe renal impairment. Candesartan has not been studied in patients with more severe renal failure (creatinine clearance < 15 mL /min).

In two studies, both including patients with mild to moderate hepatic impairment, there was an increase in the mean AUC of candesartan of approximately 20 % in one study and 80 % in the other study.

There is no experience in patients with severe hepatic impairment and/or cholestasis.

Paediatric population

The pharmacokinetic properties of candesartan were evaluated in hypertensive children aged 1 to < 6 years and 6 to < 17 years in two single dose PK studies.

In children aged 1 to < 6 years, 10 children weighing 10 to < 25 kg received a single dose of 0,2 mg/kg, oral suspension. There was no correlation between C_{max} and AUC with age or weight. No clearance data has been collected, therefore the possibility of a correlation between clearance and weight/age in this population is unknown.

In children aged 6 to < 17 years, 22 children received a single dose of a 16 mg tablet. There was no correlation between C_{max} and AUC with age. However, weight seems to significantly correlate with C_{max} (p=0.012) and AUC (p=0.011). No clearance data has been collected, therefore the possibility of a correlation between clearance and weight/age in this population is unknown.

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

The pharmacokinetics of candesartan cilexetil have not been investigated in paediatric patients <1 year of age

5.3 Preclinical safety data

There was no evidence of abnormal systemic or target organ toxicity at clinically relevant doses. In preclinical safety studies candesartan had effects on the kidneys and on red cell parameters at high doses in mice, rats, dogs and monkeys. Candesartan caused a reduction of red blood cell parameters (erythrocytes, haemoglobin, haematocrit). Effects on the kidneys (such as interstitial nephritis, tubular distension, basophilic tubules, increased plasma concentrations of urea and creatinine) were induced by candesartan which could be secondary to the

hypotensive effect leading to alterations of renal perfusion. Furthermore, candesartan induced hyperplasia / hypertrophy of the juxtaglomerular cells. These changes were considered to be caused by the pharmacological action of candesartan. For therapeutic doses of candesartan in humans, the hyperplasia / hypertrophy of the renal juxtaglomerular cells does not seem to have any relevance.

In preclinical studies in normotensive neonatal and juvenile rats, candesartan caused a reduction in body weight and heart weight. As in adult animals, these effects are considered to result from the pharmacological action of candesartan. At the lowest dose of 10 mg/kg exposure to candesartan was between 12 and 78 times the levels found in children aged 1 to < 6 who received candesartan cilexetil at a dose of 0,2 mg/kg and 7 to 54 times those found in children aged 6 to < 17 who received candesartan cilexetil at a dose of 16 mg. As a no observed effect level was not identified in these studies, the safety margin for the effects on heart weight and the clinical relevance of the finding is unknown.

Fetotoxicity has been observed in late pregnancy (see section 4.6).

Data from *in vitro* and *in vivo* mutagenicity testing indicate that candesartan will not exert mutagenic or clastogenic activities under conditions of clinical use.

There was no evidence of carcinogenicity.

The renin angiotensin aldosterone system plays a critical role in kidney development in utero. Renin angiotensin aldosterone system blockade has been shown to lead to abnormal kidney development in very young mice. Administering medicines that act directly on the renin angiotensin aldosterone system can alter normal renal development. Therefore, children aged less than 1 year should not receive candesartan (see section 4.3).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Calcium carboxymethylcellulose (carmellose calcium)

Hydroxypropyl cellulose (hyprolose)

Iron oxide reddish brown, CI 77491 (E172)

Lactose monohydrate

Magnesium stearate

Maize starch

Polyethylene glycol 8000 (macrogol).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

PVC/PVDC blisters: 3 years

HDPE bottles: 3 years

6.4 Special precautions for storage

Store at or below 30 °C.

6.5 Nature and contents of container

ATACAND 8 and 16 mg:

PVC/PVDC blister packs of 7, 14, 28, 56 or 98 tablets in strips of 7 or 30 tablets in blister strips of 10 or 15.

White HDPE bottles of 30 or 100 tablets.

ATACAND 32 mg:

PVC/PVDC blister packs of 7, 14, 28, 56 or 98 tablets in strips of 7 or 30 tablets in blister strips of 10 or 15.

White HDPE bottles of 100 tablets.

All pack sizes may not be marketed.

6.6 Special precautions for disposal

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Equity Pharmaceuticals (Pty) Ltd.

100 Sovereign Drive

Route 21 Corporate Park

Nellmapius Drive

Irene, Pretoria

South Africa

0157

8 REGISTRATION NUMBERS

ATACAND 8 mg: 32/7.1.3/0099

ATACAND 16 mg: 32/7.1.3/0100

ATACAND 32 mg: A39/7.1.3/0244

9 DATE OF FIRST AUTHORISATION / RENEWAL OF AUTHORISATION

ATACAND 8 mg: 19 March 1999

ATACAND 16 mg: 19 March 1999

ATACAND 32 mg: 08 February 2008

10 DATE OF REVISION OF TEXT

13 August 2025