

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Atacand 2 mg, 4 mg, 8 mg, 16 mg and 32 mg tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 2 mg, 4 mg, 8 mg, 16 mg or 32 mg candesartan cilexetil.

Each 2 mg tablet contains 95,4 mg lactose monohydrate.

Each 4 mg tablet contains 93,4 mg lactose monohydrate.

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

Each 16 mg tablet contains 81,4 mg lactose monohydrate.

Each 32 mg tablet contains 163 mg lactose monohydrate.

For a full list of excipients, see 6.1.

3. PHARMACEUTICAL FORM

Tablet

Atacand 2 mg are round (diameter 7 mm), white tablets.

Atacand 4 mg are round (diameter 7 mm), white tablets with a score and marked A/CF on one side and marked 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 marked 032 on the other side.

Atacand 4mg, 8 mg, 16 mg and 32 mg tablets can be divided into equal halves.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Essential hypertension.

Treatment of patients with heart failure and impaired left ventricle systolic function (left ventricular ejection fraction $\leq 40\%$) as add-on therapy to ACE inhibitors or when ACE inhibitors are not tolerated (see section 5.1 Pharmacodynamic properties).

4.2 Posology and method of administration

Dosage in Hypertension

The recommended initial dose and usual maintenance dose is 8 mg once daily. The dose may be increased to 16 mg once daily. If blood pressure is not sufficiently controlled after 4 weeks of treatment with 16 mg once daily, the dose may be further increased to a maximum of 32 mg once daily (see section 5.1 Pharmacodynamic properties). If blood pressure control is not achieved with this dose, alternative strategies should be considered.

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

Use in the elderly

No initial dosage adjustment is necessary in elderly patients.

Use in patients with intravascular volume depletion

An initial dose of 4 mg may be considered in patients at risk for hypotension, such as patients with possible volume depletion (see also 4.4 Special warnings and special precautions for use).

Use in impaired renal function

The starting dose is 4 mg in patients with renal impairment, including patients on haemodialysis. The dose should be titrated according to response. There is limited experience in patients with very severe or end-stage renal impairment ($Cl_{\text{creatinine}} < 15$ ml/min). See section 4.4 Special warnings and special precautions for use.

Use in impaired hepatic function

An initial dose of 2 mg once daily is recommended in patients with mild to moderate hepatic impairment. The dose may be adjusted according to response. There is no experience in patients with severe hepatic impairment.

Concomitant therapy

Addition of a thiazide-type diuretic such as hydrochlorothiazide has been shown to have an additive antihypertensive effect with Atacand.

Use in black patients

The antihypertensive effect of candesartan is less in black than non-black patients. Consequently, up-titration of Atacand and concomitant therapy may be more frequently needed for blood pressure control in black than non-black patients (see section 5.1 Pharmacodynamic properties).

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 warnings and special precautions for use).

Special patient populations

No initial dose adjustment is necessary for elderly patients or in patients with intravascular volume depletion, renal impairment 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 medicinal products (see also section 4.4 Special warnings and special precautions for use and 5.1 Pharmacodynamic properties).

Administration

Atacand should be taken once daily with or without food.

Use in children and adolescents

The safety and efficacy of Atacand have not been established in children and adolescents (under 18 years).

4.3 Contraindications

Hypersensitivity to candesartan cilexetil or to any of the excipients.

Pregnancy and lactation (see section 4.6 Pregnancy and lactation).

Severe hepatic impairment and/or cholestasis.

4.4 Special warnings and special precautions for use

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 renal impairment, periodic monitoring of serum potassium and creatinine levels is recommended. There is limited experience in patients with very severe or end-stage renal impairment ($Cl_{\text{creatinine}} < 15$ ml/min). 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 $>265 \mu\text{mol/L}$ ($>3 \text{ mg/dL}$).

Concomitant therapy with an ACE inhibitor in heart failure

The risk of adverse events, especially renal function impairment and hyperkalaemia, may increase when candesartan is used in combination with an ACE inhibitor (see section 4.8 Undesirable effects). Patients with such treatment should be monitored regularly and carefully.

Haemodialysis

During dialysis the blood pressure may be particularly sensitive to AT1-receptor blockade as a result of reduced plasma volume and activation of the renin-angiotensin-aldosterone system. Therefore, Atacand should be carefully titrated with thorough monitoring of blood pressure in patients on haemodialysis.

Renal artery stenosis

Other medicinal products 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.

Kidney transplantation

There is no experience regarding the administration of Atacand in patients with a 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 such as those receiving high dose diuretics. Caution should be observed when initiating therapy and correction of hypovolemia should be attempted.

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.

Aortic and mitral valve stenosis (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 medicinal products acting through inhibition of the renin-angiotensin-aldosterone system. Therefore, the use of Atacand is not recommended.

Hyperkalaemia

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

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 other medicinal products that affect this system has been associated with acute hypotension, azotaemia, oliguria or, rarely, acute renal failure. The possibility of similar effects cannot be excluded with angiotensin II receptor antagonists. As with any antihypertensive agent, excessive blood pressure decrease in patients with ischaemic cardiopathy or ischaemic cerebrovascular disease could result in a myocardial infarction or stroke.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

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

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.

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

Based on experience with the use of other medicinal products that affect the renin-angiotensin-aldosterone system, concomitant use of potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium, or other medicinal products that may increase potassium levels (e.g. heparin) may lead to increases in serum potassium.

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 and careful monitoring of serum lithium levels is recommended during concomitant use.

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

As with ACE inhibitors, concomitant use of angiotensin II receptor antagonists 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.

The bioavailability of candesartan is not affected by food.

4.6 Pregnancy and lactation

Use in pregnancy

There are very limited data from the use of Atacand in pregnant women. These data are insufficient to allow conclusions about potential risk for the fetus when used during the first trimester. In humans, foetal renal perfusion, which is dependent upon the development of the renin-angiotensin-aldosterone system, begins in the second trimester. Thus risk to the foetus increases if Atacand is administered during the second or third trimesters of pregnancy. When used in pregnancy during the second and third trimesters, medicinal products that act directly on the renin-angiotensin system can cause fetal and neonatal injury (hypotension, renal dysfunction, oliguria and/or anuria, oligohydramnios, skull hypoplasia, intrauterine growth

retardation) and death. Cases of lung hypoplasia, facial abnormalities and limb contractures have also been described.

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.

Based on the above information, Atacand should not be used in pregnancy. If pregnancy is detected during treatment, Atacand should be discontinued (see section 4.3 Contraindications).

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, Atacand should not be given during breast-feeding (see section 4.3 Contraindications).

4.7 Effects on ability to drive and use machines

The effect of candesartan on the ability to drive and use machines has not been studied, but based on its pharmacodynamic properties candesartan 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

In controlled clinical studies adverse events were mild and transient and comparable to placebo. The overall incidence of adverse events showed no association with dose or age. 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 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. The frequencies used in the tables throughout this section are: very common ($\geq 1/10$) common ($\geq 1/100 < 1/10$), uncommon ($\geq 1/1000, < 1/100$), rare ($\geq 1/10\ 000, < 1/1000$) and very rare ($< 1/10\ 000$):

System Organ Class	Frequency	Undesirable Effect
Infections and infestations	Common	Respiratory infection
Nervous system disorders	Common	Dizziness/vertigo, headache

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 decrease 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 usually necessary for patients receiving Atacand. However, in patients with renal impairment, periodic monitoring of serum potassium and creatinine levels is recommended.

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 seen were:

System Organ Class	Frequency	Undesirable Effect
Metabolism and nutrition disorders	Common	Hyperkalaemia
Vascular disorders	Common	Hypotension
Renal and urinary disorders	Common	Renal impairment

Laboratory findings

Increases in creatinine, urea and potassium. Periodic monitoring of serum creatinine and potassium is recommended (see section 4.4 Special warnings and special precautions for use).

Post Marketing

The following adverse reactions have been reported in post marketing experience:

System Organ Class	Frequency	Undesirable Effect
Blood and lymphatic system disorders	Very rare	Leukopenia, neutropenia and agranulocytosis
Metabolism and nutrition disorders	Very rare	Hyperkalaemia, hyponatraemia
Nervous system disorders	Very rare	Dizziness, headache
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, connective tissue and bone disorders	Very rare	Back pain, arthralgia, myalgia

System Organ Class	Frequency	Undesirable Effect
Renal and urinary disorders	Very rare	Renal impairment, including renal failure in susceptible patients (see section 4.4 Special warnings and special precautions for use).

4.9 Overdose

Symptoms

Based on pharmacological considerations, the main manifestation of an overdose is likely to be symptomatic hypotension and dizziness. In individual case reports of overdose (of 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 medicinal products may be administered if the above-mentioned measures are not sufficient. Candesartan is not removed by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:

Angiotensin II antagonists (candesartan), ATC code C09C A06.

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 (AT₁) receptor.

Candesartan cilexetil is a prodrug suitable for oral use. It is rapidly converted to the active substance, candesartan, by ester hydrolysis during absorption from the gastrointestinal tract. Candesartan is an angiotensin II receptor antagonist, selective for AT₁ receptors, with tight binding to and slow dissociation from the receptor. It has no agonist activity.

Candesartan does not inhibit 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 levels, angiotensin I and angiotensin II levels, and a decrease in plasma aldosterone concentration.

Hypertension

In hypertension, candesartan causes a dose-dependent, long-lasting reduction in arterial blood pressure. The antihypertensive action is due to decreased systemic peripheral resistance, without reflex increase in heart rate. 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 candesartan cilexetil, onset of antihypertensive effect generally occurs within 2 hours. With continuous treatment, most of the reduction in blood pressure with any dose is generally attained within four 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. Candesartan cilexetil once daily provides effective and smooth blood pressure reduction over 24 hours, with little difference between maximum and trough effects during the dosing interval. The antihypertensive effect and tolerability of candesartan and losartan were compared in two randomised, double-blind studies in a total of 1,268 patients with mild to moderate hypertension. The trough blood pressure reduction (systolic/diastolic) was 13.1 /10.5 mmHg with candesartan cilexetil 32 mg once daily and 10.0 /8.7 mmHg with losartan potassium 100 mg once daily (difference in blood pressure reduction 3.1/1.8 mmHg, $p<0.0001/p<0.0001$). The most common adverse events were respiratory infection (candesartan 6.6%, losartan 8.9%), headache (candesartan 5.8%, losartan 5.6%) and dizziness (candesartan 4.4%, losartan 1.9%).

When candesartan cilexetil is used together with hydrochlorothiazide, the reduction in blood pressure is additive. Concomitant administration of candesartan cilexetil with hydrochlorothiazide or amlodipine is well tolerated.

Candesartan is similarly effective in patients irrespective of age and gender.

Medicinal products 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. This is also the case for candesartan. In an open label clinical experience trial in 5,156 patients with diastolic hypertension, the blood pressure reduction during candesartan treatment was significantly less in black than non-black patients (14.4/10.3 mmHg vs 19.0/12.7 mmHg, $p<0.0001/p<0.0001$).

Candesartan 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% confidence interval 15-42%). There is currently no data on the effect of candesartan on the progression to diabetic nephropathy. In hypertensive patients with type II diabetes mellitus, 12 weeks treatment with candesartan cilexetil 8 mg to 16 mg had no adverse effects on blood glucose or lipid profile.

The effects of candesartan cilexetil 8-16 mg (mean dose 12 mg), once daily, on cardiovascular morbidity and mortality were evaluated in a randomised clinical trial with 4,937 elderly patients (aged 70-89 years; 21% aged 80 or above) with mild to moderate hypertension followed for a mean of 3.7 years (Study on COgnition and Prognosis in the Elderly). Patients received candesartan cilexetil or placebo with other antihypertensive treatment added as needed. The blood pressure was reduced from 166/90 to 145/80 mmHg in the candesartan group, and from 167/90 to 149/82 mmHg in the control group. There was no statistically significant difference in the primary endpoint, major cardiovascular events (cardiovascular mortality, non-fatal stroke and non-fatal myocardial infarction). There were 26.7 events per 1000 patient-years in the candesartan group versus 30.0 events per 1000 patient-years in the control group (relative risk 0.89, 95% CI 0.75 to 1.06, $p=0.19$).

Heart Failure

Treatment with candesartan cilexetil reduces mortality, reduces hospitalisation due to heart failure, and improves symptoms in patients with left ventricular systolic dysfunction 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 chronic heart failure (CHF) patients with NYHA functional class II to IV consisted of three separate studies: CHARM-Alternative (n=2,028) in patients with LVEF $\leq 40\%$ not treated with an ACE inhibitor because of intolerance (mainly due to cough, 72%), CHARM-Added (n=2,548) in patients with LVEF $\leq 40\%$ and treated with an ACE inhibitor, and CHARM-Preserved (n=3,023) in patients with LVEF $> 40\%$. Patients on optimal CHF therapy at baseline were randomised to placebo or candesartan cilexetil (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. After 6 months of treatment 63% of the patients still taking candesartan cilexetil (89%) were at the target dose of 32 mg.

In CHARM-Alternative, the composite endpoint of cardiovascular mortality or first CHF hospitalisation was significantly reduced with candesartan in comparison with placebo (hazard ratio (HR) 0.77, 95% CI 0.67-0.89, $p<0.001$). This corresponds to a relative risk reduction of 23%. Fourteen patients needed to be treated for the duration of the study to prevent one patient from dying of a cardiovascular event or being hospitalised for treatment of heart failure. The composite endpoint of all-cause mortality or first CHF hospitalisation was also significantly reduced with candesartan (HR 0.80,

95% CI 0.70-0.92, $p=0.001$). Both the mortality and morbidity (CHF hospitalisation) components of these composite endpoints contributed to the favourable effects of candesartan. Treatment with candesartan cilexetil resulted in improved NYHA functional class ($p=0.008$).

In CHARM-Added, the composite endpoint of cardiovascular mortality or first CHF hospitalisation was significantly reduced with candesartan in comparison with placebo (HR 0.85, 95% CI 0.75-0.96, $p=0.011$). This corresponds to a relative risk reduction of 15%. Twenty-three patients needed to be treated for the duration of the study to prevent one patient from dying of a cardiovascular event or being hospitalised for treatment of heart failure. The composite endpoint of all-cause mortality or first CHF hospitalisation was also significantly reduced with candesartan (HR 0.87, 95% CI 0.78-0.98, $p=0.021$). Both the mortality and morbidity components of these composite endpoints contributed to the favourable effects of candesartan. Treatment with candesartan cilexetil resulted in improved NYHA functional class ($p=0.020$).

In CHARM-Preserved, no statistically significant reduction was achieved in the composite endpoint of cardiovascular mortality or first CHF hospitalisation (HR 0.89, 95% CI 0.77-1.03, $p=0.118$). The numerical reduction was attributable to reduced CHF hospitalisation. There was no evidence of effect on mortality in this study.

All-cause mortality was not statistically significant when examined separately in each of the three CHARM studies. However, 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, $p=0.055$).

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

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

5.2 Pharmacokinetic properties

Absorption and distribution

Following oral administration, candesartan cilexetil is converted to the active substance 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 estimated absolute bioavailability of the tablet is therefore 14%. The

mean peak serum concentration (C_{\max}) is reached 3-4 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 to a minor extent eliminated by hepatic metabolism. 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) 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 (see section 4.2 Posology and method of administration).

In patients with mild to moderate renal impairment C_{\max} and AUC of candesartan increased during repeated dosing by approximately 50% and 70%, respectively, but $t_{1/2}$ was not altered, compared to patients with normal renal function. The corresponding changes in patients with severe renal impairment were approximately 50% and 110%, respectively. The terminal $t_{1/2}$ of candesartan was approximately doubled in patients with severe renal impairment. The 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 (see section 4.2 Posology and method of administration).

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.

Foetotoxicity has been observed in late pregnancy (see section 4.6 Pregnancy and lactation).

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

There was no evidence of carcinogenicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Carmellose calcium
Hydroxypropylcellulose
Iron oxide reddish-brown E 172 (only 8 mg, 16 mg and 32 mg tablets)
Lactose monohydrate
Magnesium stearate
Maize starch
Macrogol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years in HDPE bottles (8 mg, 16 mg and 32 mg tablets).
2 years in HDPE bottles (4 mg tablets).
3 years in PVC/PVDC blisters (4 mg, 8 mg, 16 mg and 32 mg tablets).
2 years in PVC/PVDC blisters (2 mg tablets).
3 years in polypropylene (PP) blisters (2 mg tablets).

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

2 mg tablet: PP or PVC/PVDC blister packs of 7 and 14 tablets

4 mg tablet: PVC/PVDC blister packs of 7, 14, 15, 20, 28, 30, 50, 50x1 (single dose unit), 56, 98, 98x1 (single dose unit), 100 and 300 tablets

8 mg tablet: PVC/PVDC blister packs of 7, 14, 15, 20, 28, 30, 50, 50x1 (single dose unit), 56, 98, 98x1 (single dose unit), 100 and 300 tablets

16 mg tablet: PVC/PVDC blister packs of 7, 14, 15, 20, 28, 30, 50, 50x1 (single dose unit), 56, 98, 98x1 (single dose unit), 100 and 300 tablets

32 mg tablet: PVC/PVDC blister packs of 7, 14, 15, 20, 28, 30, 50, 50x1 (single dose unit), 56, 98, 98x1 (single dose unit), 100 and 300 tablets

4 mg tablet: HDPE bottles of 100 and 250 tablets

8 mg tablet: HDPE bottles of 100 and 250 tablets

16 mg tablet: HDPE bottles of 100 and 250 tablets

32 mg tablet: HDPE bottles of 100 and 250 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

To be completed nationally.

8. MARKETING AUTHORISATION NUMBER(S)

To be completed nationally.

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

To be completed nationally.

10. DATE OF REVISION OF THE TEXT

29 January 2009