

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Candesartan Clonmel 8 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 8 mg of candesartan cilexetil.

Excipients with known effect

Each 8 mg tablet contains 49.4 mg of lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablets

Candesartan Clonmel 8 mg: 6.4 mm, round tablet of pink colour (not uniform with possible small spots of darker or white colour) with a score line on one side and a "8" on the other side.

The 4 mg, 8 mg, 16 mg tablet can be divided into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Candesartan Clonmel is indicated for the

- Treatment of primary hypertension in adults.
- Treatment of hypertension in children and adolescents aged 6 to <18 years.
- Treatment of adult patients with heart failure and impaired left ventricular systolic function (left ventricular ejection fraction \leq 40%) when Angiotensin Converting Enzyme (ACE) inhibitors are not tolerated, or as adjunctive therapy to ACE inhibitors in patients with symptomatic heart failure despite optimal therapy when mineralocorticoid receptor antagonists are not tolerated (see sections 4.2, 4.4, 4.5 and 5.1).

4.2 Posology and method of administration

Posology

Posology in hypertension

The recommended initial dose and usual maintenance dose of Candesartan Clonmel is 8 mg once daily. Most of the antihypertensive effect is attained within 4 weeks. In some patients whose blood pressure is not adequately controlled, the dose may be increased to 16 mg once daily and to a maximum of 32 mg once daily. Therapy should be adjusted according to blood pressure response.

Candesartan Clonmel may also be co-administered with other antihypertensive agents (see sections 4.3, 4.4, 4.5 and 5.1). Addition of hydrochlorothiazide has been shown to have an additive antihypertensive effect with various doses of candesartan.

Elderly

No initial dose adjustment is necessary in elderly patients.

Patients with intravascular volume depletion

An initial dose of 4 mg may be considered in patients at risk of hypotension, such as patients with possible volume depletion (see section 4.4).

Renal impairment

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 (creatinine clearance (Cl_{creatinine}) <15 ml/minute) (see section 4.4).

Hepatic impairment

An initial dose of 4 mg once daily is recommended in patients with mild to moderate hepatic impairment. The dose may be adjusted according to response. Candesartan Clonmel is contraindicated in patients with severe hepatic impairment and/or cholestasis (see sections 4.3 and 5.2).

Black patients

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

Paediatric population

Children and adolescents aged 6 to <18 years

The recommended starting dose is 4 mg once daily.

- Patients weighing < 50 kg: in patients whose blood pressure is not adequately controlled, the dose can be increased to a maximum of 8 mg once daily.
- Patients weighing ≥ 50 kg: in patients whose blood pressure is not adequately controlled, the dose can be increased to 8 mg once daily and then to 16 mg once daily, if needed (see section 5.1).

Doses above 32 mg have not been studied in paediatric patients.

Most of the antihypertensive effect is attained within 4 weeks.

For children with possible intravascular volume depletion (e.g. patients treated with diuretics, particularly those with impaired renal function), Candesartan Clonmel treatment should be initiated under close medical supervision a lower starting dose than the general starting dose mentioned above should be considered (see section 4.4).

Candesartan has not been studied in children with a glomerular filtration rate below 30 ml/min/1.73m² (see section 4.4).

Black paediatric patients

The antihypertensive effect of candesartan is less pronounced in black patients than in non-black patients (see section 5.1).

Children aged under 1 year to <6 years

- The safety and efficacy in children aged 1 to <6 years has not been established. The available data are described in section 5.1, but no dosage recommendations can be made.
- Candesartan is contraindicated in children aged below 1 year of age (see section 4.3).

Posology in heart failure

The usual recommended initial dose of Candesartan Clonmel is 4 mg once daily. Up-titration to the target dose of 32 mg once daily (maximum dose) or to the highest tolerated dose is done by doubling the dose at intervals of at least 2 weeks (see section 4.4). Evaluation of patients with heart failure should always comprise assessment of renal function, including monitoring of serum creatinine and serum potassium. Candesartan Clonmel can be administered in combination with other heart failure treatments, including ACE inhibitors, beta-blockers, diuretics and digitalis or a combination of these medicinal products. Candesartan Clonmel may be co-administered with an ACE inhibitor in patients with symptomatic heart failure despite optimal standard heart failure therapy when mineralocorticoid receptor antagonists are not tolerated. The combination of an ACE inhibitor, a potassium-sparing diuretic and Candesartan Clonmel is not recommended and should be considered only after careful evaluation of the potential benefits and risks (see sections 4.4, 4.8 and 5.1).

Special patient populations

Not initial dose adjustment is necessary for elderly patients or in patients with intravascular volume depletion or renal impairment or mild to moderate hepatic impairment.

Paediatric population

The safety and efficacy of Candesartan Clonmel in children aged between birth and 18 years have not been established in the treatment of heart failure. No data are available.

Method of administration

Oral use.

Candesartan Clonmel should be taken once a day with or without food.

Bioavailability of candesartan is not affected by food.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Second and third trimester of pregnancy (see points 4.4 and 4.6).

Severe hepatic impairment and/or cholestasis.

Children aged below 1 year of age (see section 5.3).

The concomitant use of Candesartan Clonmel with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m²) (see sections 4.5 and 5.1).

4.4 Special warnings and precautions for use

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

There is evidence that concomitant use of ACE inhibitors and 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 ACE inhibitors with angiotensin II receptor blockers or aliskiren is therefore not recommended (see sections 4.5 and 5.1).

If dual blockade therapy is considered absolutely necessary, this should only be 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.

Renal impairment

As with other medicinal products inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible patients treated with Candesartan Clonmel.

When Candesartan Clonmel 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_{creatinine} < 15 mL/minute). In these patients, Candesartan Clonmel should be carefully titrated with careful monitoring of blood pressure.

Evaluation of patients with heart failure should include periodic assessment of renal function, especially in elderly patients aged 75 years or older and patients with impaired renal function. During dose titration of Candesartan Clonmel, monitoring of serum creatinine and serum potassium is recommended. Clinical trials in heart failure did not include patients with serum creatinine > 265 µmol/l (> 3 mg/dl).

Paediatric population, including paediatric patients with renal impairment

Candesartan has not been studied in children with a glomerular filtration rate of less than 30 ml/min/1.73m² (see section 4.2).

Concomitant treatment with ACE inhibitors in heart failure

The risk of side effects, especially hypotension, hyperkalaemia and decreased renal function (including acute renal failure) may be increased when Candesartan Clonmel is used in combination with an ACE inhibitor. Triple combination of an ACE inhibitor, a mineralocorticoid receptor antagonist and candesartan is also not recommended. Use of these combinations should be under the 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.

Hemodialysis

During dialysis, blood pressure may be particularly sensitive to AT1 receptor blockade as a result of reduce plasma volume and activation of the renin-angiotensin-aldosterone system. Therefore, Candesartan Clonmel 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, including angiotensin II receptor antagonists (AIIAs), may increase blood urea and serum creatinine in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney.

Kidney transplantation

There is limited clinical evidence regarding candesartan uses in patients who have undergone renal transplant.

Hypotension

Hypotension may occur during treatment with Candesartan Clonmel in heart failure patients. 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 hypovolaemia should be attempted.

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

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 so severe such that it may warrant the use of intravenous fluids and/or vasopressor therapy.

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 valves 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 Candesartan Clonmel is not recommended in this population.

Hyperkalaemia

Concomitant use of Candesartan Clonmel and potassium-sparing diuretics, potassium supplements, salt substitutes potassium-containing, or other medicinal product that may increase potassium levels (for example, heparin, combinations of trimethoprim/sulfamethoxazole) may lead to increase in serum potassium in hypertensive patients. Monitoring of serum potassium should be undertaken as appropriate.

In heart failure patients treated with Candesartan Clonmel, hyperkalaemia may occur. Periodic monitoring of serum potassium is recommended. The combination of an ACE inhibitor, a potassium-sparing diuretic (for example spironolactone) and Candesartan Clonmel is not recommended and should be considered only after careful evaluation of the potential benefits and risks.

Intestinal angioedema

Intestinal angioedema has been reported in patients treated with angiotensin II receptor antagonists, including candesartan (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 should be discontinued, and appropriate monitoring should be initiated until complete resolution of symptoms has occurred.

General

In patients whose vascular tonus and renal function depend predominantly activity of the renin-angiotensin-aldosterone system (for example, 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, azotemia, oliguria or, rarely, acute renal failure. The possibility of similar effects cannot be excluded for AIIAs. As with other antihypertensive agents, an 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 candesartan may be enhanced by other medical products with blood pressure-lowering properties, whether prescribed as an antihypertensives or for other indications.

Pregnancy

AllIRAs should not be initiated during pregnancy. Unless continued AllIRA therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use during pregnancy. When pregnancy is diagnosed, treatment with AllIRAs should be stopped immediately and if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

In post-menarche patients, the possibility of pregnancy should be on a regularly 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).

Candesartan Clonmel Contains lactose

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

4.5 Interaction with other medicinal products and other forms of interaction

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

Concomitant use of potassium-sparing diuretics, potassium supplements, salt substitute potassium-containing or other medicinal products (for example, heparin) may increase potassium levels. Monitoring of potassium should be undertaken as appropriate (see section 4.4).

Reversible increases in serum lithium concentrations and toxicity have been reported with during concomitant administration of lithium and ACE inhibitors. A similar effect may occur with AllIRAs. Use of candesartan with lithium is not recommended. If the combination proves necessary, careful monitoring of serum lithium levels is recommended.

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

As with ACE inhibitors, concomitant use of AllIRAs and NSAIDs may lead in an increased risk of worsening 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 of renal function should be considered after initiation of concomitant therapy and periodically thereafter.

Clinical trial data has shown that dual blocked of the renin-angiotensin-aldosterone system (RAAS) by through the combined use of ACE inhibitors, angiotensin II receptor blockers or aliskiren is associated with a higher incidence of adverse events such as hypotension, hyperkalaemia and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting drug (see sections 4.3, 4.4 and 5.1).

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactationPregnancy

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

Epidemiological studies on the risk of teratogenicity associated with ACE inhibitor therapy in the first trimester of pregnancy has not been conclusive; however, a small increase risk cannot be excluded. Although there are no controlled epidemiological data on the risk of AllIRAs, there may be similar risks for this group of medicinal products. Unless continued treatment with AllIRAs is considered absolutely necessary, patients planning to become pregnant should switch to an alternative antihypertensive treatment with an established safety profile for use during pregnancy. Once pregnancy is established, AllIRA treatment should be discontinued immediately, and other treatment should be initiated if appropriate.

AllRA treatment in the second and third trimester is known to cause human fetotoxicity (impaired renal function, oligohydramnios, delayed ossification of the skull) and neonatal toxicity (renal failure, hypotension, hyperkalaemia) (see section 5.3).

In case of exposure to AllRAs in the second or third trimester of pregnancy, ultrasound scanning of renal function and skull is recommended.

Children whose mothers have taken AllRAs should be closely monitored for hypotension (see sections 4.3 and 4.4).

Breast-feeding

As there is no information on the use of candesartan during lactation, Candesartan Clonmel is not recommended. Other treatments with better established safety profiles during lactation are recommended, especially in breast-feeding newborn or premature infants.

4.7 Effects on ability to drive and use machines

No studies have been conducted on the effect of candesartan on the ability to drive and operate machinery. However, it should be taken into account that occasionally dizziness and weariness may occur with Candesartan Clonmel.

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 or age. Withdrawals from of treatment due to adverse events was similar for candesartan cilexetil (3.1%) and placebo (3.2%).

In a pooled analysis of clinical trial data of hypertensive patients, adverse reactions to candesartan cilexetil were defined 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 shows adverse reactions from clinical trials and post-marketing experience.

The frequencies used in the tables in section 4.8 are: Very common ($\geq 1/10$), Common ($\geq 1/100$ to $< 1/10$), Uncommon ($\geq 1/1000$ to $< 1/100$), Rare ($\geq 1/10,000$ to $< 1/1000$), very rare ($< 1/10,000$) and not known (cannot be estimated from the available data).

System organ classes	Frequency	Adverse reaction
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	Increase in liver enzymes, abnormal liver function or hepatitis
Skin and subcutaneous tissues 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

In general, there were no clinically important influences of candesartan on routinely measured laboratory variables. As for other inhibitors of the renin-angiotensin-aldosterone system, small decreases in haemoglobin were seen. No routine monitoring of laboratory variables is usually necessary in patients treated with Candesartan Clonmel. However, in patients with renal impairment, regular monitoring of serum potassium and creatinine level is recommended in patients.

Pediatric population

The safety of candesartan cilexetil was monitored in 255 hypertensive children and adolescents aged 6 to <18 years during a 4-week clinical efficacy study and a 1-year unblinded study (see section 5.1). Within almost all of the different system organ classes, the frequency of adverse events in children is within the common/non-common range. While the nature and severity of

adverse reactions are comparable to that seen in adults (see table above), the frequency of all adverse reactions is higher in children and adolescents, particularly in:

- Headache, dizziness, and upper respiratory infection are "very common" (i.e. $\geq 1/10$) in children and "common" ($\geq 1/100$ 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. $\geq 1/100$ to $< 1/10$) in children and "very rare" ($< 1/10,000$) in adults.
- Hyperkalaemia, hyponatraemia and abnormal liver function are "uncommon" ($\geq 1/1,000$ to $< 1/100$) in children and "very rare" ($< 1/10,000$) in adults.
- Sinus arrhythmia, nasopharyngitis and pyrexia are "common" (i.e. $> 1/100$ to $< 1/10$) and oropharyngeal pain is "very common" (i.e. $\geq 1/10$) in children but not reported in adults. However, these are transient and common childhood diseases.

The overall safety profile of candesartan cilexetil in paediatric patients is not significantly different from the safety profile in adults.

Treatment of heart failure

The adverse experience profile of candesartan in adult patients with heart failure was consistent with the pharmacology of the drug and the health status of the patients. In the CHARM clinical trial programme, comparing candesartan cilexetil up to 32 mg (n=3,803) with placebo (n=3,796), 21.0% of the candesartan cilexetil group and 16.1% of the placebo group discontinued treatment due to adverse events. The most frequently reported adverse events were hyperkalaemia, hypotension and renal impairment.

These adverse reactions were more frequent in patients over 70 years of age, in diabetics and in patients receiving other medicinal products affecting the renin-angiotensin-aldosterone system, in particular an ACE inhibitor and/or spironolactone.

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

System organ class	Frequency	Adverse reaction
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
Respiratory, thorax 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 liver function or hepatitis
Skin and subcutaneous tissues disorders	Very rare	Angioedema, rash, urticaria, itching
Musculoskeletal and connective tissue disorders	Very rare	Back pain, arthralgia, myalgia, myalgia
Renal and urinary disorders	Common	Impaired renal function, including renal failure in predisposed patients (see section 4.4)

Laboratory findings

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Website: www.hpra.ie.

4.9 Overdose

Symptoms

Based on pharmacological considerations, the main manifestation of overdose is likely to be symptomatic hypotension and dizziness. In individual reports of overdose (with up to 672 mg of candesartan cilexetil) in adults, patients recovered was uneventful.

Treatment

If symptomatic hypotension should occur, symptomatic treatment should be instituted, and vital signs monitored. The patient should be placed in the supine position 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 given if the above measures are not sufficient.

Candesartan is not removed by haemodialysis.

5 PHARMACOLOGICAL PROPERTIES**5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Angiotensin II antagonists, plain ATC code: C 09 CA 06

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 (AT₁) receptor.

Pharmacodynamic effect

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 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 levels, angiotensin I and angiotensin II levels, and a decrease in plasma aldosterone concentration.

Clinical efficacy and safetyHypertension

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, $p < 0.0001/p < 0.0001$).

When candesartan cilexetil is used together with hydrochlorothiazide, the reduction in blood pressure is additive. An increased antihypertensive effect is also seen when candesartan cilexetil is combined with amlodipine or felodipine.

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 does not affect or increases glomerular filtration rate,

while renal vascular resistance and filtration fraction are reduced. In a 3-month clinical study of hypertensive patients with type 2 diabetes and microalbuminuria, antihypertensive treatment with candesartan cilexetil reduced urinary albumin excretion (albumin/creatinine ratio, mean: 30% with 95% confidence interval: 15-42%). No data are currently available on the effect of candesartan on progression to diabetic nephropathy.

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).

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 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.

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 1 to <6 years, 93 patients, 74% of whom had renal disease, were randomised to receive an oral dose of candesartan cilexetil suspension 0.05, 0.20 or 0.40 mg/kg once daily. The primary method of analysis was slope of the change in systolic blood pressure (SBP) as a function of dose. SBP and diastolic blood pressure (DBP) decreased 6.0/5.2 to 12.0/11.1 mmHg from baseline across the three doses of candesartan cilexetil. However, since there was no placebo group, the true magnitude of blood pressure effect remains uncertain which makes a conclusive assessment of benefit-risk balance difficult in this age group.

In children aged 6 to <17 years, 240 patients were randomised to receive either placebo or low, medium, or high doses of candesartan cilexetil in a ratio of 1: 2: 2: 2. For children who weighed < 50 kg, the doses of candesartan cilexetil were 2, 8, or 16 mg once daily. In children who weighed > 50 kg, the candesartan cilexetil doses were 4, 16 or 32 mg once daily. Candesartan at pooled doses reduced SiSBP by 10.2 mmHg (P < 0.0001) and SiDBP (P=0.0029) by 6.6 mmHg, from the base line. In the placebo group, there was also a reduction of 3.7 mmHg in SiSBP (p=0.0074) and 1.80 mmHg for SiDBP (p=0.0992) from the baseline. Despite the large placebo effect, all individual candesartan doses (and all doses pooled) were significantly superior to placebo. Maximum response in reduction of blood pressure in children below and above 50 kg was reached at 8 mg and 16 mg doses, respectively and the effect plateaued after that point.

Of those enrolled, 47% were black patients and 29% were female; mean age +/- SD was 12.9 +/- 2.6 years. 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

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 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 to 0.89, $p < 0.001$). This corresponds to a relative risk reduction of 23%. Of candesartan patients 33.0% (95%CI: 30.1 to 36.0) and of placebo patients 40.0% (95%CI: 37.0 to 43.1) experienced this endpoint, absolute difference 7.0% (95%CI: 11.2 to 2.8). 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 to 0.92, $p=0.001$). Of candesartan patients 36.6% (95%CI: 33.7 to 39.7) and of placebo patients 42.7% (95%CI: 39.6 to 45.8) experienced this endpoint, absolute difference 6.0% (95%CI: 10.3 to 1.8). 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 to 0.96, $p=0.011$). This corresponds to a relative risk reduction of 15%. Of candesartan patients 37.9% (95%CI: 35.2 to 40.6) and of placebo patients 42.3% (95%CI: 39.6 to 45.1) experienced this endpoint, absolute difference 4.4% (95%CI: 8.2 to 0.6). 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 to 0.98, $p=0.021$). Of candesartan patients 42.2% (95%CI: 39.5 to 45.0) and of placebo patients 46.1% (95%CI: 43.4 to 48.9) experienced this endpoint, absolute difference 3.9% (95%CI: 7.8 to 0.1). 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 to 1.03, $p=0.118$).

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 to 0.98, $p=0.018$) and all three studies, HR 0.91 (95%CI: 0.83 to 1.00, $p=0.055$).

The beneficial effects of candesartan 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 into 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 compared to the oral solution is approximately 34% with very little variability. The estimated absolute bioavailability of the tablet is therefore 14 %. The mean maximum serum concentration (C_{max}) is reached within 3-4 hours after tablet ingestion. The serum concentration of candesartan increases linearly with increasing doses within the therapeutic dose range.

No sex-related difference in candesartan pharmacokinetics has been observed. The area under the curve serum concentration versus time curve (AUC) of candesartan is not significantly affected by food.

Candesartan is highly bound to plasma proteins (> 99%). The apparent volume of distribution of candesartan is 0,1 l/kg.

Bioavailability of candesartan is not affected by food intake.

Biotransformation and elimination

Candesartan is mainly eliminated unchanged via the urine and bile and only to a minor extent eliminated 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 medicinal products whose metabolism depends on the 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 a renal clearance of about 0.19 mL/min/kg. Renal elimination of candesartan occurs is both by glomerular filtration and via active tubular secretion. Following a single oral dose of ¹⁴C-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 elderly subjects (> 65 years), the C_{max} and AUC of candesartan are increased by approximately 50% and 80%, respectively, compared to younger subjects. However, the in blood pressure response and the incidence of adverse events are similar after a given dose of candesartan are similar in younger and older patients (see section 4.2).

In patients with mild to moderate renal impairment, the C_{max} and AUC of candesartan increased after 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 $t_{1/2}$ for candesartan was approximately doubled in patients with severe renal impairment. The AUC of candesartan in patients on haemodialysis was similar to that seen in patients with severe renal impairment.

In two studies, both including patients with mild to moderate hepatic impairment, there was an increase in mean AUC for candesartan of approximately 20% in one study and 80% in the other (see section 4.2). There is no experience in patients with severe hepatic impairment.

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 oral suspension dose of 0.2 mg/kg. There was no correlation between C_{max} and AUC with respect to age or weight. No clearance data were collected and 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 16 mg tablet as a single dose. There was no correlation between C_{max} and AUC with age. However, weight seems to significant correlate with C_{max} ($p=0.012$) and AUC ($p=0.011$). No clearance data has been collected and therefore the possibility of a relationship between clearance and weight/age in this population is unknown.

Children aged >6 years had an exposure similar to adults given the same dose.

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

5.3 Preclinical safety data

There was no evidence of abnormal systemic or target organ toxicity at clinically relevant doses. In high dose preclinical safety studies, candesartan affected the kidneys and red blood cells in mice, rats, dogs and monkeys. Candesartan caused a reduction in 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 and could be secondary to the hypotensive effect causing changes in renal blood flow. Furthermore, candesartan induced hyperplasia/hypertrophy of the juxtaglomerular cells. These changes are thought to be induced by the pharmacological effects

of candesartan. It does not appear that hyperplasia/hypertrophy of the juxtaglomerular cells has any relevance in humans at therapeutic doses of candesartan.

In preclinical studies with normotensive neonatal and juvenile rats, candesartan caused a reduction in body weight and heart weight. As in adult animals, these effects are thought to be due to the pharmacological action of candesartan. At the lowest dose of 10 mg/kg, exposure to candesartan was between 12 and 78 times higher than the levels found in children aged 1 to <6 given candesartan cilexetil at a dose of 0.2 mg/kg and 7 to 54 times higher than the levels found in children aged 6 to <17 given a dose of 16 mg candesartan cilexetil. As no no observed effect level (NOEL) was identified in these studies, the margin of safety for the effect on heart weight and the clinical relevance of this finding are unknown.

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

Data from *in vitro* and *in vivo* mutagenicity studies suggest that candesartan will not exert mutagenic or clastogenic activity in clinical use.

There was no evidence of carcinogenicity.

The renin angiotensin aldosterone system plays an important role in renal development in utero. Renin angiotensin aldosterone system blockade has been shown to cause abnormal kidney development in very young mice. Administration of medicinal products that act directly on the renin angiotensin aldosterone system may alter normal kidney development. Therefore, children aged less than 1 year of age should not receive candesartan (see section 4.3).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Maize starch
Hydroxypropylcellulose
Carmellose calcium
Macrogol 8000
Magnesium stearate
Red iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Tablets are available in:

8 mg pack-sizes:

PVC/Aluminium blister: 14, 20, 28, 30, 50, 56, 84, 90, 98, 100 tablets
HDPE bottles with PP cap with an integrated silica gel desiccant: 100 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Clonmel Healthcare Ltd
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E91 D768
Ireland

8 MARKETING AUTHORISATION NUMBER

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 31st January 2025

10 DATE OF REVISION OF THE TEXT