SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

<[Invented name]> 8 mg/5 mg tablets
<[Invented name]> 16 mg/10 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

<[Invented name]> 8 mg/5 mg: Each tablet contains 8 mg candesartan cilexetil and 5 mg amlodipine (as amlodipine besilate).
<[Invented name]> 16 mg/10 mg: Each tablet contains 16 mg candesartan cilexetil and 10 mg amlodipine (as amlodipine besilate).

Excipient(s) with known effect: lactose monohydrate and sodium.

<[Invented name]> 8 mg/5 mg: Each tablet contains 60.9 mg lactose monohydrate and 0.19 mg sodium.
<[Invented name]> 16 mg/10 mg: Each tablet contains 121.9 mg lactose monohydrate and 0.38 mg sodium.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet
<[Invented name]> 8 mg/5 mg: White to off-white, round biconvex tablets, with a diameter approx. 6 mm embossed with „8“ on one side and „5“ on the other side.
<[Invented name]> 16 mg/10 mg: White to off-white, round biconvex tablets with a diameter approx. 8 mm, with halving score on both sides, embossed with „16 16“ on one side and „10 10“ on the other side. The tablet can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

<[Invented name]> is indicated as substitution therapy in adult patients with essential hypertension whose blood pressure is adequately controlled with amlodipine and candesartan given concurrently at the same dose level.

4.2 Posology and method of administration

Posology
Patients should use the strength corresponding to their previous treatment.
For the usual doses different strengths of this medicinal product are available.
A dose of 8 mg candesartan cilexetil and 5 mg amlodipine daily is given as 1 tablet of <[Invented name]> 8 mg/5 mg.

A dose of 16 mg candesartan cilexetil and 10 mg amlodipine daily is given as 2 tablets of <[Invented name]> 8 mg/5 mg or 1 tablet of <[Invented name]> 16 mg/10 mg.
The maximum daily dose of candesartan cilexetil is 32 mg and the maximum daily dose of amlodipine is 10 mg .

Elderly (aged 65 years or over)
Caution is required when increasing the dosage (see sections 4.4 and 5.2).

Hepatic impairment
Dosage recommendations for patients with impaired liver function have not been established <[Invented name]> is contraindicated in patients with severe hepatic impairment and in patients with cholestasis (see sections 4.3, 4.4 and 5.2).

Renal impairment
No dosage adjustment is required for patients with mild to moderate renal impairment (with creatinine clearance > 15 ml/min, see sections 4.4 and 5.2). Monitoring of potassium levels and creatinine is advised in moderate renal impairment.

Paediatric population
The safety and efficacy of <[Invented name]> in children aged below 18 years has not yet been established. No data are available.

Method of administration
The tablets can be taken with or without food.

4.3 Contraindications

- Hypersensitivity to the active substances, dihydropyridine derivatives or to any of the excipients listed in section 6.1.
- Severe hypotension
- Shock, including cardiogenic shock
- Obstruction of the outflow tract of the left ventricle (e.g. high grade aortic stenosis).
- Haemodynamically unstable heart failure after acute myocardial infarction
- Second and third trimesters of pregnancy (see sections 4.4 and 4.6).
- Severe hepatic impairment and/or cholestasis.
- The concomitant use of <[Invented name]> with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m^2) (see sections 4.5 and 5.1).

4.4 Special warnings and precautions for use

Amlodipine
The safety and efficacy of amlodipine in hypertensive crisis has not been established.

Cardiac failure
Patients with heart failure should be treated with caution. In a long-term, placebo controlled study in patients with severe heart failure (NYHA class III and IV) the reported incidence of pulmonary oedema was higher in the amlodipine treated group than in the placebo group (see section 5.1).

Calcium channel blockers, including amlodipine, should be used with caution in patients with congestive heart failure, as they may increase the risk of future cardiovascular events and mortality.

Hepatic impairment
The half life of amlodipine is prolonged and AUC values are higher in patients with impaired liver function; dosage recommendations have not been established. Amlodipine should therefore be initiated at the lower end of the dosing range and caution should be used, both on initial treatment and when increasing the dose. Slow dose titration and careful monitoring may be required in patients with severe hepatic impairment.

Elderly
In the elderly increase of the dosage should take place with care (see sections 4.2 and 5.2).

Renal failure
Amlodipine may be used in such patients at normal doses. Changes in amlodipine plasma concentrations are not correlated with degree of renal impairment. Amlodipine is not dialysable.

Candesartan

Renal impairment
As with other agents inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible patients treated with candesartan.
When candesartan 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/min). In these patients candesartan 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 candesartan, monitoring of serum creatinine and potassium is recommended. Clinical trials in heart failure did not include patients with serum creatinine > 265 μmol/l (> 3 mg/dl).

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)
There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE-inhibitors, 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 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."

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, candesartan should be carefully titrated with thorough monitoring of blood pressure in patients on haemodialysis.

Renal artery stenosis
Medicinal products that affect the renin-angiotensin-aldosterone system, including angiotensin II receptor antagonists (AIIRAs), 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 use in patients who have undergone renal transplant.

Hypotension
Hypotension may occur during treatment with candesartan 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 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 candesartan is not recommended in this population.

Hyperkalaemia
Concomitant use of candesartan with potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium, or other medicinal products that may increase potassium levels (e.g. heparin, co-trimoxazole also known as trimethoprim/sulfamethoxazole) may lead to increases in serum potassium in hypertensive patients. Monitoring of potassium should be undertaken as appropriate.
In heart failure patients treated with candesartan, hyperkalaemia may occur. Periodic monitoring of serum potassium is recommended. The combination of an ACE inhibitor, a potassium-sparing diuretic (e.g. spironolactone) and candesartan is not recommended and should be considered only after careful evaluation of the potential benefits and risks.

General
In patients whose vascular tone and renal function depend predominantly on the activity of the reninangiotensin-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 AIIRAs. 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.

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.

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

Warning about excipients
This medicine contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the total lactase deficiency or glucose-galactose malabsorption should not take this medicine.
This medicine contains less than 1 mmol sodium (23 mg) per tablet; that is to say essentially "sodium-free".

4.5 Interaction with other medicinal products and other forms of interaction

Interactions linked to amlodipine

Effects of other medicinal products on amlodipine

CYP3A4 inhibitors
Concomitant use of amlodipine with strong or moderate CYP3A4 inhibitors (protease inhibitors, azole antifungals, macrolides like erythromycin or clarithromycin, verapamil or diltiazem) may give rise to significant increase in amlodipine exposure resulting in an increased risk of hypotension. The clinical translation of these PK variations may be more pronounced in the elderly. Close clinical observation of patients is recommended and dose adjustment may thus be required.

CYP3A4 inducers
Upon co-administration of known inducers of the CYP3A4, the plasma concentration of amlodipine may vary. Therefore, blood pressure should be monitored and dose regulation considered both during and after concomitant medication particularly with strong CYP3A4 inducers (e.g. rifampicin, *hypericum perforatum*).

Administration of amlodipine with grapefruit or grapefruit juice is not recommended as bioavailability may be increased in some patients resulting in increased blood pressure lowering effects.

Dantrolene (infusion)
In animals, lethal ventricular fibrillation and cardiovascular collapse are observed in association with hyperkalemia after administration of verapamil and intravenous dantrolene. Due to risk of hyperkalemia, it is recommended that the co-administration of calcium channel blockers such as amlodipine be avoided in patients susceptible to malignant hyperthermia and in the management of malignant hyperthermia.

Effects of amlodipine on other medicinal products

The blood pressure lowering effects of amlodipine adds to the blood pressure-lowering effects of other medicinal products with antihypertensive properties.

In clinical interaction studies, amlodipine did not affect the pharmacokinetics of atorvastatin, digoxin or warfarin.

Tacrolimus
There is a risk of increased tacrolimus blood levels when co administered with amlodipine. In order to avoid toxicity of tacrolimus, administration of amlodipine in a patient treated with tacrolimus requires monitoring of tacrolimus blood levels and dose adjustment of tacrolimus when appropriate.

Mechanistic Target of Rapamycin (mTOR) Inhibitors
mTOR inhibitors such as sirolimus, temsirolimus, and everolimus are CYP3A substrates. Amlodipine is a weak CYP3A inhibitor. With concomitant use of mTOR inhibitors, amlodipine may increase exposure of mTOR inhibitors.

Cyclosporine
No drug interaction studies have been conducted with cyclosporine and amlodipine in healthy volunteers or other populations with the exception of renal transplant patients, where variable trough concentration increases (average 0% - 40%) of cyclosporine were observed. Consideration should be given for monitoring cyclosporine levels in renal transplant patients on amlodipine, and cyclosporine dose reductions should be made as necessary.

Simvastatin
Co-administration of multiple doses of 10 mg of amlodipine with 80 mg simvastatin resulted in a 77% increase in exposure to simvastatin compared to simvastatin alone. Limit the dose of simvastatin to 20 mg daily in patients on amlodipine.

Interactions linked to candesartan

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)
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 (including acute renal failure) compared to the use of a single RAAS-acting agent (see sections 4.3, 4.4 and 5.1).

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

NSAIDs

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.

Potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium and other substances that may increase potassium levels
Concomitant use of potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium, or other medicinal products (e.g. heparin) may increase potassium levels. Monitoring of potassium should be undertaken as appropriate (see section 4.4).

Active substances 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.

4.6 Fertility, pregnancy and lactation

Pregnancy
<[Invented name]> is not recommended during the first trimester of pregnancy as no data are available and safety profile has not been established for both amlodipine and candesartan. Use in early pregnancy is only recommended when there is no safer alternative and when the disease itself carries greater risk for the mother and foetus.
<[Invented name]> is contraindicated during the second and third trimesters of pregnancy due to candesartan content.

Amlodipine
The safety of amlodipine in human pregnancy has not been established. In animal studies, reproductive toxicity was observed at high doses (see section 5.3).

Candesartan
The use of AIIRAs is not recommended during the first trimester of pregnancy (see section 4.4). The use of AIIRAs is contraindicated during the second and third trimesters of pregnancy (see sections 4.3 and 4.4).
Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Whilst there is no controlled epidemiological data on the risk with AIIRAs, similar risks may exist for this class of active substances. Unless continued AIIRA therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with AIIRAs should be stopped immediately and, if appropriate, alternative therapy should be started.
Exposure to AIIRA therapy during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia) (see section 5.3).

Should exposure to AIIRAs have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended. Infants whose mothers have taken AIIRAs should be closely observed for hypotension (see sections 4.3 and 4.4).

Breast-feeding
Amlodipine is excreted in human milk. The proportion of the maternal dose received by the infant has been estimated with an interquartile range of 3 – 7%, with a maximum of 15%. The effect of amlodipine on infants is unknown. No information is available regarding the use of candesartan during breast-feeding. Therefore, <[Invented name]> is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while breast-feeding a newborn or preterm infant.

Fertility
Amlodipine
Reversible biochemical changes in the head of spermatozoa have been reported in some patients treated by calcium channel blockers. Clinical data are insufficient regarding the potential effect of amlodipine on fertility. In one rat study, adverse effects were found on male fertility (see section 5.3).

Candesartan
Animal studies have shown that candesartan cilexetil had no adverse effect on fertility in rats (see section 5.3)

4.7 Effects on ability to drive and use machines

<[Invented name]> has moderate influence on the ability to drive and use machines. If patients taking <[Invented name]> suffer from dizziness, headache, fatigue or nausea the ability to react may be impaired. Caution is recommended especially at the start of treatment.

4.8 Undesirable effects

Adverse reactions previously reported with one of the individual components (amlodipine or candesartan) may be potential undesirable effects with <[Invented name]>.

Undesirable effects linked to amlodipine

Summary of the safety profile
The most commonly reported adverse reactions during treatment are somnolence, dizziness, headache, palpitations, flushing, abdominal pain, nausea, ankle swelling, oedema and fatigue.

The following adverse reactions have been observed and reported during treatment with amlodipine with the following frequencies: 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).
Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

System organ class	**Frequency**	**Adverse reactions**
Blood and lymphatic system	Very rare	Leukocytopenia, thrombocytopenia

disorders		
Immune system disorders	Very rare	Allergic reactions
Metabolism and nutrition disorders	Very rare	Hyperglycaemia
Psychiatric disorders	Uncommon	Depression, mood changes (including anxiety), insomnia
	Rare	Confusion
Nervous system disorders	Common	Somnolence, dizziness, headache (especially at the beginning of the treatment)
	Uncommon	Tremor, dysgeusia, syncope, hypoaesthesia, paraesthesia
	Very rare	Hypertonia, peripheral neuropathy
	Not known	Extrapyramidal disorder
Eye disorders	Common	Visual disturbance (including diplopia)
Ear and labyrinth disorders	Uncommon	Tinnitus
Cardiac disorders	Common	Palpitations
	Uncommon	Arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation)
	Very rare	Myocardial infarction
Vasuclar disorders	Common	Flushing
	Uncommon	Hypotension
	Very rare	Vasculitis
Respiratory, thoracic and mediastinal disorders	Common	Dyspnoea
	Uncommon	Cough, rhinitis
Gastrointestinal disorders	Common	Abdominal pain, nausea, dyspepsia, altered bowel habits (including diarrhoea and constipation)
	Uncommon	Vomiting, dry mouth
	Very rare	Pancreatitis, gastritis, gingival hyperplasia
Hepato-biliary disorders	Very rare	Hepatitis, jaundice, hepatic enzymes increased*
Skin and subcutaneous tissue disorders	Uncommon	Alopecia, purpura, skin discolouration, hyperhidrosis, pruritus, rash, exanthema, urticaria
	Very rare	Angioedema, erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, Quincke oedema, photosensitivity
	Not known	Toxic epidermal necrolysis
Musculoskeletal and connective tissue disorders	Common	Ankle swelling, muscle cramps
	Uncommon	Arthralgia, myalgia, back pain
Renal and urinary disorders	Uncommon	Micturition disorder, nocturia, increased urinary frequency
Reproductive system and breast disorders	Uncommon	Impotence, gynecomastia
General disorders and administration site conditions	Very common	Oedema
	Common	Fatigue, asthenia
	Uncommon	Chest pain, pain, malaise

Investigations	Uncommon	Weight increased, weight decreased

*mostly consistent with cholestasis

Undesirable effects linked to candesartan

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 treatment due to adverse events were similar with candesartan cilexetil (3.1%) and placebo (3.2%).

In a pooled analysis of clinical trial data of hypertensive patients, adverse reactions with 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 presents adverse reactions from clinical trials and post-marketing experience. The frequencies used in the tables throughout section 4.8 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) and 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
Gastrointestinal disorders	Very rare	Nausea
	Not known	Diarrhoea
Respiratory, thoracic and mediastinal disorders	Very rare	Cough
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
In general, there were no clinically important influences of candesartan on routine laboratory variables. As for other inhibitors of the renin-angiotensin-aldosterone system, small decreases in haemoglobin have been seen. No routine monitoring of laboratory variables is usually necessary for patients receiving candesartan cilexetil. However, in patients with renal impairment, periodic monitoring of serum potassium and creatinine levels is recommended.

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 the national reporting system listed in Appendix V.

4.9 Overdose

Symptoms
There is no experience of overdose with <[Invented name]>. The major symptom of overdose with candesartan is possibly pronounced hypotension with dizziness. Overdose with amlodipine may result in excessive peripheral vasodilation and, possibly, reflex tachycardia. Marked and potentially prolonged systemic hypotension up to and including shock with fatal outcome have been reported.
In individual case reports of candesartan overdose (of up to 672 mg candesartan cilexetil) patient recovery was uneventful.

Management
If ingestion is recent, induction of vomiting or gastric lavage may be considered. Administration of activated charcoal to healthy volunteers immediately or up to two hours after ingestion of amlodipine 10 mg has been shown to reduce the absorption rate of amlodipine. Clinically significant hypotension due to <[Invented name]> overdose calls for active cardiovascular support, including frequent monitoring of cardiac and respiratory function, elevation of extremities, and attention to circulating fluid volume and urine output. A vasoconstrictor may be helpful in restoring vascular tone and blood pressure, provided that there is no contraindication to its use. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade.

Both candesartan and amlodipine are unlikely to be removed by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Agents acting on the renin-angiotensin system, angiotensin II antagonists and calcium channel blockers
ATC code: C09DB07

<[Invented name]> combines two antihypertensive compounds with complementary mechanisms to control blood pressure in patients with essential hypertension: amlodipine belongs to the calcium antagonist class and candesartan to the angiotensin II antagonist class of medicines. The combination of these substances has an additive antihypertensive effect, reducing blood pressure to a greater degree than either component alone.

Amlodipine
Amlodipine is a calcium ion influx inhibitor of the dihydropyridine group (slow channel blocker or calcium ion antagonist) and inhibits the transmembrane influx of calcium ions into cardiac and vascular smooth muscle.

The mechanism of the antihypertensive action of amlodipine is due to a direct relaxant effect on vascular smooth muscle. The precise mechanism by which amlodipine relieves angina has not been fully determined but amlodipine reduces total ischaemic burden by the following two actions:

Amlodipine dilates peripheral arterioles and thus, reduces the total peripheral resistance (afterload) against which the heart works. Since the heart rate remains stable, this unloading of the heart reduces myocardial energy consumption and oxygen requirements.

The mechanism of action of amlodipine also probably involves dilatation of the main coronary arteries and coronary arterioles, both in normal and ischaemic regions. This dilatation increases myocardial oxygen delivery in patients with coronary artery spasm (Prinzmetal's or variant angina).

In patients with hypertension, once daily dosing provides clinically significant reductions of blood pressure in both the supine and standing positions throughout the 24 hour interval. Due to the slow onset of action, acute hypotension is not a feature of amlodipine administration.

Amlodipine has not been associated with any adverse metabolic effects or changes in plasma lipids and is suitable for use in patients with asthma, diabetes, and gout.

Candesartan

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 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 AT_1 receptors, with tight binding to and slow dissociation from the receptor. It has no agonist activity.

Candesartan does not inhibit ACE, which converts angiotensin I to angiotensin II and degrades bradykinin. 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 (AT_1) 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 safety

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

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 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 is currently no data on the effect of candesartan on the 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 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.

5.2 Pharmacokinetic properties

Absorption and distribution

Amlodipine
After oral administration of therapeutic doses, amlodipine is well absorbed with peak blood levels between 6-12 hours post dose. Absolute bioavailability has been estimated to be between 64 and 80%. The volume of distribution is approximately 21 l/kg. In vitro studies have shown that approximately 97.5% of circulating amlodipine is bound to plasma proteins.
The bioavailability of amlodipine is not affected by food intake.

Candesartan
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.
The bioavailability of candesartan is not affected by food.

Biotransformation/elimination

Amlodipine
The terminal plasma elimination half life is about 35-50 hours and is consistent with once daily dosing. Amlodipine is extensively metabolised by the liver to inactive metabolites with 10% of the parent compound and 60% of metabolites excreted in the urine.

Candesartan
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 drugs whose metabolism is dependent upon cytochrome P450 isoenzymes CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1 or CYP3A4. The terminal half-life of candesartan is approximately 9 hours. There is no accumulation following multiple doses. Total plasma clearance of candesartan is about 0.37 ml/min/kg, with a renal clearance of about 0.19 ml/min/kg. The renal elimination of candesartan is both by glomerular filtration and active tubular secretion. Following an oral dose of 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

Hepatic impairment
Amlodipine
Very limited clinical data are available regarding amlodipine administration in patients with hepatic impairment. Patients with hepatic insufficiency have decreased clearance of amlodipine resulting in a longer half-life and an increase in AUC of approximately 40-60%.

Candesartan
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 (see section 4.2). There is no experience in patients with severe hepatic impairment.

Elderly
Amlodipine
The time to reach peak plasma concentrations of amlodipine is similar in elderly and younger subjects. Amlodipine clearance tends to be decreased with resulting increases in AUC and elimination half-life in elderly patients. Increases in AUC and elimination half-life in patients with congestive heart failure were as expected for the patient age group studied.

Candesartan
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 candesartan in young and elderly patients (see section 4.2).

Renal impairment
Amlodipine
Changes in amlodipine plasma concentrations are not correlated with degree of renal impairment. Amlodipine is not dialysable.

Candesartan
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 t½ 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 t½ 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.

5.3 Preclinical safety data

Amlodipine

Reproductive toxicology

Reproductive studies in rats and mice have shown delayed date of delivery, prolonged duration of labour and decreased pup survival at dosages approximately 50 times greater than the maximum recommended dosage for humans based on mg/kg.

Impairment of fertility

There was no effect on the fertility of rats treated with amlodipine (males for 64 days and females 14 days prior to mating) at doses up to 10 mg/kg/day (8 times* the maximum recommended human dose of 10 mg on a mg/m^2 basis). In another rat study in which male rats were treated with amlodipine besilate for 30 days at a dose comparable with the human dose based on mg/kg, decreased plasma follicle-stimulating hormone and testosterone were found as well as decreases in sperm density and in the number of mature spermatids and Sertoli cells.

Carcinogenesis, mutagenesis

Rats and mice treated with amlodipine in the diet for two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 mg/kg/day showed no evidence of carcinogenicity. The highest dose (for mice, similar to, and for rats twice* the maximum recommended clinical dose of 10 mg on a mg/m^2 basis) was close to the maximum tolerated dose for mice but not for rats.
Mutagenicity studies revealed no drug related effects at either the gene or chromosome levels.
*Based on patient weight of 50 kg

Candesartan

Foetotoxicity has been observed in late pregnancy (see section 4.6).
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.
There was no evidence of carcinogenicity with candesartan.
Data from *in vitro* and *in vivo* mutagenicity testing indicates, that candesartan will not exert mutagenic or clastogenic activities under conditions of clinical use.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydroxypropylcelullose
Lactose monohydrate
Croscarmellose sodium
Maize starch
Triethyl citrate
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store below 30°C.
Store in the original package in order to protect from light.

6.5 Nature and contents of container

PVC/PE/PVDC//Al blisters
Pack size: 14, 28, 30, 56, 84, 90 or 98 tablets

Not all sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

<[To be completed nationally]>
{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

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

<{MM/YYYY}>
<[To be completed nationally]>

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

<[Invented name]> 8 mg/5 mg tablets
<[Invented name]> 16 mg/10 mg tablets
Candesartan cilexetil/amlodipine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

<[Invented name]> 8 mg/5 mg: Each tablet contains 8 mg candesartan cilexetil and 5 mg amlodipine (as amlodipine besilate).
<[Invented name]> 16 mg/10 mg: Each tablet contains 16 mg candesartan cilexetil and 10 mg amlodipine (as amlodipine besilate).

3. LIST OF EXCIPIENTS

Contains lactose monohydrate and sodium. See the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Tablet
14 tablets
28 tablets
30 tablets
56 tablets
84 tablets
90 tablets
98 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store below 30°C.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

<[To be completed nationally]>
(MAH, city, country)

12. MARKETING AUTHORISATION NUMBER(S)

<[To be completed nationally]>

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

<[To be completed nationally]>

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

<[Invented name]> 8 mg/5 mg
<[Invented name]> 16 mg/10 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

<2D barcode carrying the unique identifier included>

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

<[Invented name]> 8 mg/5 mg tablets
<[Invented name]> 16 mg/10 mg tablets
Candesartan cilexetil/amlodipine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

<[To be completed nationally]>
(MAH logo)

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. OTHER

Package leaflet: Information for the patient

<[Invented name]> 8 mg/5 mg tablets
<[Invented name]> 16 mg/10 mg tablets
Candesartan cilexetil/amlodipine

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What <[Invented name]> is and what it is used for

<[Invented name]> contains two substances called amlodipine and candesartan. Both of these substances help to control high blood pressure.
- Amlodipine belongs to a group of substances called "calcium channel blockers". Amlodipine stops calcium from moving into the blood vessel wall which stops the blood vessels from tightening.
- Candesartan belongs to a group of substances called "angiotensin-II receptor antagonists". Angiotensin II is produced by the body and makes the blood vessels tighten, thus increasing the blood pressure. Candesartan works by blocking the effect of angiotensin II.

This means that both of these substances help to stop the blood vessels tightening. As a result, the blood vessels relax and blood pressure is lowered.

<[Invented name]> is used to treat high blood pressure in patients whose blood pressure is already controlled on the combination of amlodipine and candesartan taken separately at the same doses as in <[Invented name]>

2. What you need to know before you take <[Invented name]>

Do not take <[Invented name]>
- if you are allergic to amlodipine or to any other calcium antagonists, candesartan cilexetil or any of the other ingredients of this medicine (listed in section 6).

- if you have severe low blood pressure (hypotension)
- if you have narrowing of the aortic heart valve (aortic stenosis) or cardiogenic shock (a condition where your heart is unable to supply enough blood to the body).
- if you suffer from heart failure after a heart attack
- if you are more than 3 months pregnant. (see pregnancy section)
- if you have severe liver disease or biliary obstruction (a problem with the drainage of the bile from the gall bladder)
- if you have diabetes or impaired kidney function and you are treated with a blood pressure lowering medicine containing aliskiren.

Warnings and precautions
Talk to your doctor or pharmacist before taking <[Invented name]> if you have or have had any of the following conditions:
- recent heart attack
- heart failure
- severe increase in blood pressure (hypertensive crisis)
- low blood pressure (hypotension)
- you are elderly and your dose needs to be increased
- liver or kidney problems, or are on dialysis
- if you have recently had a kidney transplant
- if you are vomiting, have recently had severe vomiting, or have diarrhoea
- if you have a disease of the adrenal gland called Conn's syndrome (also called primary hyperaldosteronism)
- if you have ever had a stroke
- if you are going to receive an anesthestic. This may be given for an operation or any dental work.
- if you are taking any of the following medicines used to treat high blood pressure:
  - an ACE-inhibitor (for example enalapril, lisinopril, ramipril), in particular if you have diabetes-related kidney problems.
  - aliskiren

Your doctor may check your kidney function, blood pressure, and the amount of electrolytes (e.g. potassium) in your blood at regular intervals.
See also information under the heading "Do not take <[Invented name]>".

You must tell your doctor if you think you are (or might become) pregnant. <[Invented name]> is not recommended in early pregnancy, and must not be taken if you are more than 3 months pregnant, as it may cause serious harm to your baby if used at that stage (see pregnancy section).

Children and adolescents
There is no experience with the use of <[Invented name]> in children (below the age of 18 years). Therefore, do not give this medicineto children and adolescents.

Other medicines and <[Invented name]>
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

<[Invented name]> may affect or be affected by other medicines. Your doctor may need to change your dose and/or to take other precautions if you are taking:

- ketoconazole, itraconazole (anti-fungal medicines)
- ritonavir, indinavir, nelfinavir (so called protease inhibitors used to treat HIV)
- rifampicin, erythromycin, clarithromycin (antibiotics - for infections caused by bacteria)
- hypericum perforatum (St. John's Wort)
- verapamil, diltiazem (heart medicines)
- dantrolene (infusion for severe body temperature abnormalities)
- tacrolimus, sirolimus, temsirolimus, and everolimus (used to control your body's immune response, enabling your body to accept the transplanted organ)
- simvastatin (a cholesterol lowering medicine)
- cyclosporine (an immunosuppressant)
- other medicines to help lower your blood pressure, including beta-blockers and diazoxide
- an ACE-inhibitor or aliskiren (see also information under the headings "Do not take" <[Invented name]> and "Warnings and precautions")
- non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, naproxen, diclofenac, celecoxib or etoricoxib (medicines to relieve pain and inflammation)
- acetylsalicylic acid (medicine to relieve pain and inflammation), if you are taking more than 3 g each day.
- potassium supplements or salt substitutes containing potassium (medicines that increase the amount of potassium in your blood)
- heparin (a medicine for thinning the blood)
- co-trimoxazole (an antibiotic medicine) also known as trimethoprim/sulfamethoxazole
- water tablets (diuretics)
- lithium (a medicine for mental health problems)

<[Invented name]> with food and drink
Grapefruit juice and grapefruit should not be consumed while taking <[Invented name]>. This is because grapefruit and grapefruit juice can lead to an increase in the blood levels of the active ingredient amlodipine, which can cause an unpredictable increase in the blood pressure lowering effect of <[Invented name]>.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Pregnancy
You must tell your doctor if you think you are (or might become) pregnant. Your doctor will normally advise you to stop taking <[Invented name]> before you become pregnant or as soon as you know you are pregnant and will advise you to take another medicine instead of <[Invented name]>. <[Invented name]> is not recommended in early pregnancy, and must not be taken when more than 3 months pregnant, as it may cause serious harm to your baby if used after the third month of pregnancy.

Breast-feeding
Amlodipine has been shown to pass into breast milk in small amounts. If you are breastfeeding or about to start breast-feeding you must tell your doctor before taking <[Invented name]>. <[Invented

name]> is not recommended for mothers who are breast-feeding, and your doctor may choose another treatment for you if you wish to breast-feed, especially if your baby is newborn, or was born prematurely.

Driving and using machines
<[Invented name]> may have moderate influence on your ability to drive or use machines. If the tablets make you feel sick, dizzy or tired, or give you a headache, do not drive or use machines and contact your doctor immediately.

<[Invented name]> contains lactose monohydrate and sodium
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially "sodium-free".

3. How to take <[Invented name]>

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

The recommended dose of <[Invented name]> 8 mg/5 mg is 1 or 2 tablets daily.
The recommended dose of <[Invented name]> 16 mg/10 mg is 1 tablet daily.
You can take <[Invented name]> with or without food.

If you take more <[Invented name]> than you should
Taking too many tablets may cause your blood pressure to become low or even dangerously low. You may feel dizzy, lightheaded, faint or weak. If blood pressure drop is severe enough shock can occur. Your skin could feel cool and clammy and you could lose consciousness. Seek immediate medical attention if you take too many tablets.

If you forget to take <[Invented name]>
If you forget to take a tablet, leave out that dose completely. Take your next dose at the right time. Do not take a double dose to make up for a forgotten dose.

If you stop taking <[Invented name]>
Your doctor will advise you how long to take your medicine. Your condition may return if you stop using your medicine before you are advised. Therefore do not stop taking <[Invented name]> without first talking to your doctor.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Visit your doctor **immediately** if you experience any of the following, very rare, severe side effects after taking this medicine:

- sudden wheeziness, chest pain, shortness of breath or difficulty in breathing
- swelling of eyelids, face or lips
- swelling of the tongue and throat which causes great difficulty breathing
- severe skin reactions including intense skin rash, hives, reddening of the skin over your whole body, severe itching, blistering, peeling and swelling of the skin, inflammation of mucous membranes (Stevens Johnson Syndrome, toxic epidermal necrolysis) or other allergic reactions
- heart attack, abnormal heart beat
- inflamed pancreas which may cause severe abdominal and back pain accompanied with feeling very unwell

Candesartan may cause a reduction in number of white blood cells. Your resistance to infection may be decreased and you may notice tiredness, an infection or a fever. If this happens contact your doctor. Your doctor may occasionally do blood tests to check whether <[Invented name]> has had any effect on your blood (agranulocytosis).

Other possible side effects:

Since <[Invented name]> is a combination of two active substances, the side effects that have been reported are linked either to the use of amlodipine or candesartan.

Side effects linked to the use of amlodipine

Very common (may affect more than 1 in 10 people):

- oedema (fluid retention)

Common (may affect up to 1 in 10 people):

- headache, dizziness, sleepiness (especially at the beginning of treatment)
- palpitations (awareness of your heart beat), flushing
- abdominal pain, feeling sick (nausea)
- altered bowel habits, diarrhoea, constipation, indigestion
- tiredness, weakness
- visual disturbances, double vision
- muscle cramps
- ankle swelling

Uncommon (may affect up to 1 in 100 people):

- mood changes, anxiety, depression, sleeplessness
- trembling, taste abnormalities, fainting
- numbness or tingling sensation in your limbs; loss of pain sensation
- ringing in the ears
- low blood pressure
- sneezing/running nose caused by inflammation of the lining of the nose (rhinitis)
- cough

- dry mouth, vomiting (being sick)
- hair loss, increased sweating, itchy skin, red patches on skin, skin discolouration
- disorder in passing urine, increased need to urinate at night, increased number of times of passing urine
- inability to obtain an erection; discomfort or enlargement of the breasts in men
- pain, feeling unwell
- joint or muscle pain, back pain
- weight increase or decrease

Rare (may affect up to 1 in 1,000 people):
- confusion

Very rare (may affect up to 1 in 10,000 people):
- decreased numbers of white blood cells, decrease in blood platelets which may result in unusual bruising or easy bleeding (red blood cell damage)
- excess sugar in blood (hyperglycaemia)
- a disorder of the nerves which can cause muscular weakness, tingling or numbness
- swelling of the gums
- abdominal bloating (gastritis)
- abnormal liver function, inflammation of the liver (hepatitis), yellowing of the skin (jaundice), liver enzyme increase which may have an effect on some medical tests
- increased muscle tension
- inflammation of blood vessels, often with skin rash
- sensitivity to light

Not known (frequency cannot be estimated from the available data):
- trembling, rigid posture, mask-like face, slow movements and a shuffling, unbalanced walk

Side effects linked to the use of candesartan

Common (may affect up to 1 in 10 people):
- feeling dizzy/spinning sensation
- headache
- respiratory infection
- low blood pressure. This may make you feel faint or dizzy.
- changes in blood test results: an increased amount of potassium in your blood, especially if you already have kidney problems or heart failure. If this is severe you may notice tiredness, weakness, irregular heart beat or pins and needles.
- effects on how your kidneys work, especially if you already have kidney problems or heart failure. In very rare cases, kidney failure may occur.

Very rare (may affect up to 1 in 10,000 people):
- swelling of the face, lips, tongue and/or throat
- a reduction in your red or white blood cells. You may notice tiredness, an infection or a fever
- skin rash, lumpy rash (hives)

- itching
- back pain, pain in joints and muscles
- changes in how your liver is working, including inflammation of the liver (hepatitis). You may notice tiredness, yellowing of your skin and the whites of your eyes and flu like symptoms.
- cough
- nausea
- changes in blood test results: a reduced amount of sodium in your blood. If this is severe then you may notice weakness, lack of energy, or muscle cramps.

Not known (frequency cannot be estimated from the available data):
- diarrhoea.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store <[Invented name]>

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton/blister after EXP. The expiry date refers to the last day of that month.

Store below 30°C. Store in the original package in order to protect from light.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What <[Invented name]> contains

The active substances are candesartan cilexetil and amlodipine.
<[Invented name]> 8 mg/5 mg: Each tablet contains 8 mg candesartan cilexetil and 5 mg amlodipine (as amlodipine besilate).
<[Invented name]> 16 mg/10 mg: Each tablet contains 16 mg candesartan cilexetil and 10 mg amlodipine (as amlodipine besilate).

The other ingredients are hydroxypropylcelullose, lactose monohydrate, croscarmellose sodium, maize starch, triethyl citrate, magnesium stearate.

What <[Invented name]> looks like and contents of the pack

<[Invented name]> 8 mg/5 mg: White to off-white, round biconvex tablets, embossed with „8“ on one side and „5“ on the other side.
<[Invented name]> 16 mg/10 mg: White to off-white, round biconvex tablets with halving score on both sides, embossed with „16 16“ on one side and „10 10“ on the other side.
The tablet can be divided into equal doses.

Pack size: 14, 28, 30, 56, 84, 90 or 98 tablets

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

<[To be completed nationally]>
{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

This medicinal product is authorised in the Member States of the EEA under the following names:

Cyprus, Greece, Romania, Czech Republic, Poland, Germany	Caramlo
Estonia, Latvia, Lithuania, Hungary	Zenicamo
Portugal	CARZAP AM
Bulgaria	Карамло

This leaflet was last revised in <{MM/YYYY}>
<[To be completed nationally]>