

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

[Invented name] 8 mg + 5 mg, capsules, hard
[Invented name] 8 mg + 10 mg, capsules, hard
[Invented name] 16 mg + 5 mg, capsules, hard
[Invented name] 16 mg + 10 mg, capsules, hard

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 8 mg candesartan cilexetil and 5 mg amlodipine equivalent to 6.935 mg amlodipine besilate.
Each capsule contains 8 mg candesartan cilexetil and 10 mg amlodipine equivalent to 13.87 mg amlodipine besilate.
Each capsule contains 16 mg candesartan cilexetil and 5 mg amlodipine equivalent to 6.935 mg amlodipine besilate.
Each capsule contains 16 mg candesartan cilexetil and 10 mg amlodipine equivalent to 13.87 mg amlodipine besilate.

Excipient with known effect:

Each capsule contains 101.95 mg of lactose monohydrate.
Each capsule contains 211.90 mg of lactose monohydrate.
Each capsule contains 203.90 mg of lactose monohydrate.
Each capsule contains 203.90 mg of lactose monohydrate.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsule, hard

[Invented name] 8 mg + 5 mg, capsules, hard: hard gelatin capsules, size no. 3, white opaque body, dark yellow cap, filled with white to off white granulate

[Invented name] 8 mg + 10 mg, capsules, hard: hard gelatin capsules, size no. 1, white opaque body with black imprint CAN 8, yellow cap with black imprint AML 10, filled with white to off white granulate

[Invented name] 16 mg + 5 mg, capsules, hard: hard gelatin capsules, size no. 1, white opaque body with black imprint CAN 16, pale yellow cap with black imprint AML 5, filled with white to off white granulate

[Invented name] 16 mg + 10 mg, capsules, hard: hard gelatin capsules, size no. 1, white opaque body, white opaque cap, filled with white to off white granulate

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Posology

Replacement therapy, adults

1 capsule per day. Patients should use the strength corresponding to their previous treatment with candesartan and amlodipine as separate products

Special populations

Elderly

No dose adjustment is necessary for elderly patients. Caution is required when increasing the dosage. Little information is available in the very elderly patients.

Patients with renal impairment (see also section 4.4)

No dosage adjustment is required for patients with mild to moderate renal impairment. Monitoring of potassium levels and creatinine is advised in moderate renal impairment. Limited experience is available in patients with severe or end-stage renal impairment (Clcr <15 mL/min) or haemodialysis. Caution is advised. Changes in amlodipine plasma concentrations are not correlated with degree of renal impairment, therefore the normal dosage is recommended. Amlodipine and candesartan cilexetil are not dialysable.

Patients with hepatic impairment

In patients with mild to moderate hepatic impairment [Invented name] should be administered with caution. [Invented name] is contraindicated in patients with severe hepatic impairment and/or cholestasis (see sections 4.3, 4.4 and 5.2).

Paediatric population

The safety and efficacy of [Invented name] in children aged below 18 years have not been established. No data are available.

Methods of administration

Oral route.

[Invented name] can be taken with or without food. It is recommended to take [Invented name] with some liquid.

4.3 Contraindications

- Hypersensitivity to the active substances, to dihydropyridine derivatives, or to any of the excipients (see section 6.1);
- Second and third trimesters of pregnancy (see sections 4.4 and 4.6);
- Biliary obstructive disorders and severe hepatic impairment;
- Shock (including cardiogenic shock);
- Severe hypotension;
- Obstruction of the outflow-tract of the left ventricle (e.g. high grade aortic stenosis)
- Haemodynamically unstable heart failure after acute myocardial infarction;
- 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 m²) (see sections 4.5 and 5.1).

4.4 Special warnings and precautions for use

Pregnancy

Angiotensin II receptor antagonists should not be initiated during pregnancy. Unless continued angiotensin II receptor antagonist 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 angiotensin II receptor antagonists should

be stopped immediately, and, if appropriate, alternative therapy should be started (see section 4.3 and 4.6).

Hepatic impairment

Amlodipine half-life is prolonged and AUC values are higher in patients with impaired liver function; dose recommendations have not been established. [Invented name] should therefore be used with caution in these patients. [Invented name] is contraindicated in patients with severe hepatic impairment (see section 4.3)

Renovascular hypertension

There is an increased risk of severe hypotension and renal insufficiency when patients with bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney when treated with medicinal products that affect the renin-angiotensin-aldosterone system.

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 ($Cl_{\text{creatinine}} < 15 \text{ ml/min}$). 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 $> 265 \mu\text{mol/l}$ ($> 3 \text{ mg/dl}$).

Haemodialysis

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

Kidney transplantation

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

Intravascular hypovolaemia

Symptomatic hypotension, especially after the first dose, may occur in patients who are volume and/or sodium depleted by e.g. vigorous diuretic therapy, dietary salt restriction, diarrhoea or vomiting. Such conditions should be corrected before the administration of candesartan. If hypotension occurs with [Invented name], the patient should be placed in the supine position and, if necessary, given an intravenous infusion of normal saline. Treatment can be continued once blood pressure has been stabilised.

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.

Other conditions with stimulation of the renin-angiotensin-aldosterone system

In patients whose vascular tone and renal function depend predominantly on the activity of the renin-angiotensin-aldosterone system (e.g. patients with severe congestive heart failure or underlying renal disease, including renal artery stenosis), treatment with medicinal products that affect this system has been associated with acute hypotension, hyperazotaemia, oliguria, or rarely acute renal failure (see section 4.8). As with any antihypertensive medicinal product, excessive reduction of blood pressure in patients with ischaemic cardiomyopathy or ischaemic cardiovascular disease could result in a myocardial infarction or stroke.

Primary aldosteronism

Patients with primary aldosteronism generally will not respond to antihypertensive medicinal products acting through inhibition of the renin-angiotensin system. Therefore, the use of candesartan is not recommended.

Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy

As with other vasodilators, special caution is indicated in patients suffering from aortic or mitral stenosis, or obstructive hypertrophic cardiomyopathy.

Unstable angina pectoris, acute myocardial infarction

There are no data to support the use of [Invented name] in unstable angina pectoris and during or within one month of a myocardial infarction.

Hypertensive crisis

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

Patients with 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.

Concomitant therapy with an ACE-inhibitor in heart failure

The risk of adverse reactions, especially hypotension, hyperkalaemia and decreased renal function (including acute renal failure), may increase when [Invented name] 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 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.

Hyperkalaemia

The use of medicinal products that affect the renin-angiotensin-aldosterone system may cause hyperkalaemia. Hyperkalaemia may be fatal in the elderly, in patients with renal insufficiency, in diabetic patients, in patients concomitantly treated with other medicinal products that may increase potassium levels, and/or in patients with intercurrent events.

Before considering the concomitant use of medicinal products that affect the renin-angiotensin aldosterone system, the benefit risk ratio should be evaluated. The main risk factors for hyperkalaemia to be considered are:

- Diabetes mellitus,
- Renal impairment,
- Age (>70 years),

- Combination with one or more other medicinal products that affect the renin-angiotensin aldosterone system and/or potassium supplements.

- Salt substitutes containing potassium,
- Potassium-sparing diuretics, ACE inhibitors, angiotensin II receptor antagonists, nonsteroidal anti-inflammatory medicinal products (NSAIDs, including selective COX-2 inhibitors), heparin, immunosuppressives (cyclosporin or tacrolimus), and trimethoprim.
- Intercurrent events, in particular dehydration, acute cardiac decompensation, metabolic acidosis, worsening of renal function, sudden worsening of the renal condition (e.g. infectious diseases), cellular lysis (e.g. acute limb ischemia, rhabdomyolysis, extend trauma).

Serum potassium should be monitored closely in these patients (see section 4.5).

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.

Precautions for use

Excipients:

Due to the presence of lactose, patients with rare hereditary problems of galactose intolerance, glucose galactose malabsorption, or the Lapp lactase deficiency should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

No interactions between the two components of this fixed dose combinations have been observed in clinical studies.

Interactions common to the combination.

No drugs interaction studies have been performed.

To be taken into account with concomitant use

Other antihypertensive medicinal products

The blood pressure lowering effect of [Invented name] can be increased by concomitant use of other antihypertensive medicinal products.

Medicinal products with blood pressure lowering potential

Based on their pharmacological properties it can be expected that the following medicinal products may potentiate the hypotensive effects of all antihypertensives including [Invented name], e.g. baclofen, amifostine, neuroleptics or antidepressants. Furthermore, orthostatic hypotension may be aggravated by alcohol.

Corticosteroids (systemic route)

Reduction of the antihypertensive effect.

Interactions linked to candesartan

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.

Potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium, or other medicinal products (e.g. heparin) 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).

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.

Dual blockade of the renin-angiotensin-aldosterone-system

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).”

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. The clinical translation of these PK variations may be more pronounced in the elderly. Clinical monitoring and dose adjustment may thus be required.

Clarithromycin is an inhibitor of CYP3A4. There is an increased risk of hypotension in patients receiving clarithromycin with amlodipine. Close observation of patients is recommended when amlodipine is co administered with clarithromycin.

CYP3A4 inducers

~~There is no data available regarding the effect of CYP3A4 inducers on amlodipine. The concomitant use of CYP3A4 inducers (e.g., rifampicin, hypericum perforatum) may give a lower plasma concentration of amlodipine. Amlodipine should be used with caution together with 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).

Dantrolene (infusion)

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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.

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.

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 in patients on amlodipine to 20 mg daily.

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

4.6 Fertility, pregnancy and lactation

Pregnancy

Linked to 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 drugs. 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).

Linked to 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).

Use in pregnancy is only recommended when there is no safer alternative and when the disease itself carries greater risk for the mother and foetus.

Breast-feeding

Linked to Candesartan

Because no information is available regarding the use of candesartan during breastfeeding, it is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.

Linked to Amlodipine

~~It is not known whether amlodipine is excreted in breast milk.~~ 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. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with amlodipine should be made taking into account the benefit of breast-feeding to the child and the benefit of amlodipine therapy to the mother.

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Fertility

Linked to 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).

4.7 Effects on ability to drive and use machines

No studies on the effects of candesartan on the ability to drive and use machines have been performed. However, it should be taken into account that occasionally dizziness or weariness may occur during treatment with candesartan.

Amlodipine can have minor or moderate influence on the ability to drive and use machines. If patients taking amlodipine 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

Fixed dose combination

No clinical studies have been performed. Undesirable effect observed for particular active ingredients are described below.

Adverse reactions previously reported with one of the individual components (candesartan or amlodipine) may be potential adverse reactions with [Invented name] as well, even if not observed in clinical trials or during the post-marketing period.

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 cilixetil (3.1%) and placebo (3.2%).

In a pooled analysis of clinical trial data of hypertensive patients, adverse reactions with candesartan cilixetil were defined based on an incidence of adverse events with candesartan cilixetil 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 ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$) and very rare ($< 1/10,000$).

System Organ Class	Frequency	Undesirable Effect
Infections and infestations	Common	Respiratory infection
Blood and lymphatic system disorders	Very rare	Leukopenia, neutropenia and agranulocytosis
Metabolism and nutrition disorders	Very rare	Hyperkalaemia, hyponatraemia
Nervous system disorders	Common	Dizziness/vertigo, headache
Respiratory, thoracic and mediastinal disorders	Very rare	Cough
Gastrointestinal disorders	Very rare	Nausea
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

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. However, in patients with renal impairment, periodic monitoring of serum potassium and creatinine levels is recommended.

Amlodipine

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

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

System organ class	Frequency	Adverse reactions
Blood and lymphatic system disorders	Very rare	Leukocytopenia, thrombocytopenia
Immune system disorders	Very rare	Allergic reactions
Metabolism and nutrition disorders	Very rare	Hyperglycaemia
Psychiatric disorders	Uncommon	Insomnia, mood changes (including anxiety), depression
	Rare	Confusion
Nervous system disorders	Common	Somnolence, dizziness,

		headache (especially at the beginning of the treatment)
	Uncommon	Tremor, dysgeusia, syncope, hypoesthesia, paresthesia
	Very rare	Hypertonia, peripheral neuropathy
	Not known	Extrapyramidal disorder
Eye disorders	Uncommon	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
Vascular 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
Hepatobiliary 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, urticaria, exfoliative dermatitis, Stevens-Johnson syndrome, Quincke oedema, photosensitivity
	<u>Unknown</u>	<u>Toxic Epidermal Necrolysis</u>
Musculoskeletal and connective tissue disorders	Common	Ankle swelling
	Uncommon	Arthralgia, myalgia, muscle cramps, back pain
Renal and urinary disorders	Uncommon	Micturition disorder, nocturia, increased urinary frequency
Reproductive system and breast disorders	Uncommon	Impotence, gynaecomastia
General disorders and administration site	Very common	Oedema
	Common	Fatigue, asthenia

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conditions	Uncommon	Chest pain, pain, malaise
Investigations	Uncommon	Weight increase, weight decrease

*mostly consistent with cholestasis

Exceptional cases of extrapyramidal syndrome have been reported.

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

In humans experience with intentional overdose is limited.

Symptoms

Available data suggest that gross overdosage of amlodipine could result in excessive peripheral vasodilatation and possibly reflex tachycardia. Marked and probably prolonged systemic hypotension up to and including shock with fatal outcome have been reported.

Based on pharmacological considerations, the main manifestation of an overdose of candesartan is likely to be symptomatic hypotension and dizziness. In individual case reports of overdose (of up to 672mg candesartan cilexetil) patient recovery was uneventful.

Treatment

If symptomatic hypotension should occur, symptomatic treatment should be instituted and vital signs monitored. The patient should be placed supine with the legs elevated. If this is not sufficient, plasma volume should be increased by infusion of, for example, isotonic saline solution. Sympathomimetic medicinal products may be administered if the above-mentioned measures are not sufficient. Candesartan is not removed by haemodialysis.

Clinically significant hypotension due to amlodipine overdosage 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.

Gastric lavage may be worthwhile in some cases. In healthy volunteers the use of charcoal up to 2 hours after administration of amlodipine 10 mg has been shown to reduce the absorption rate of amlodipine.

Since amlodipine is highly protein-bound, dialysis is not likely to be of benefit.

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: an angiotensin II receptor antagonist, candesartan cilexetil and a dihydropyridinic calcium channel blocker, amlodipine.

The combination of these substances has an additive antihypertensive effect, reducing blood pressure to a greater degree than either component alone.

Candesartan cilexetil

Angiotensin II is the primary vasoactive hormone of the renin-angiotensin-aldosterone system and plays a role in the pathophysiology of hypertension, heart failure and other cardiovascular disorders. It also has a role in the pathogenesis of end organ hypertrophy and damage. The major physiological effects of angiotensin II, such as vasoconstriction, aldosterone stimulation, regulation of salt and water homeostasis and stimulation of cell growth, are mediated via the type 1 (AT1) receptor.

Candesartan cilexetil is a prodrug suitable for oral use. It is rapidly converted to the active substance, candesartan, by ester hydrolysis during absorption from the gastrointestinal tract. Candesartan is an 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.

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 hypertension 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.

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:

- 1) 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.
- 2) 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).

Pharmacodynamic effects

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.

In patients with angina, once daily administration of amlodipine increases total exercise time, time to angina onset, and time to 1 mm ST segment depression, and decreases both angina attack frequency and glyceryl trinitrate tablet consumption.

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.

Use in Patients with Heart Failure

Haemodynamic studies and exercise based controlled clinical trials in NYHA Class II-IV heart failure patients have shown that amlodipine did not lead to clinical deterioration as measured by exercise tolerance, left ventricular ejection fraction and clinical symptomatology.

A placebo controlled study (PRAISE) designed to evaluate patients in NYHA Class III-IV heart failure receiving digoxin, diuretics and ACE inhibitors has shown that amlodipine did not lead to an increase in risk of mortality or combined mortality and morbidity with heart failure.

In a follow-up, long term, placebo controlled study (PRAISE-2) of amlodipine in patients with NYHA III and IV heart failure without clinical symptoms or objective findings suggestive of underlying ischaemic disease, on stable doses of ACE inhibitors, digitalis, and diuretics, amlodipine had no effect on total cardiovascular mortality. In this same population it was associated with increased reports of pulmonary oedema.

Treatment to prevent heart attack trial (ALLHAT)

A randomized double-blind morbidity-mortality study called the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart

Attack Trial (ALLHAT) was performed to compare newer drug therapies: amlodipine 2.5-10 mg/d (calcium channel blocker) or lisinopril 10-40 mg/d (ACE-inhibitor) as first-line therapies to that of the thiazide-diuretic, chlorthalidone 12.5-25 mg/d in mild to moderate hypertension. A total of 33,357 hypertensive patients aged 55 or older were randomized and followed for a mean of 4.9 years. The patients had at least one additional CHD risk factor, including: previous myocardial infarction or stroke (> 6 months prior to enrollment) or documentation of other atherosclerotic CVD (overall 51.5%), type 2 diabetes (36.1%), HDL-C < 35 mg/dL (11.6%), left ventricular hypertrophy diagnosed by electrocardiogram or echocardiography (20.9%), current cigarette smoking (21.9%).

The primary endpoint was a composite of fatal CHD or non-fatal myocardial infarction. There was no significant difference in the primary endpoint between amlodipine-based therapy and chlorthalidone-based therapy: RR 0.98 95% CI(0.90-1.07) p=0.65.

Among secondary endpoints, the incidence of heart failure (component of a composite combined cardiovascular endpoint) was significantly higher in the amlodipine group as compared to the chlorthalidone group (10.2% vs 7.7%, RR 1.38, 95% CI [1.25-1.52] p<0.001). However, there was no significant difference in all-cause mortality between amlodipine-based therapy and chlorthalidone-based therapy. RR 0.96 95% CI [0.89-1.02] p=0.20.

5.2 Pharmacokinetic properties

Candesartan cilexetil

Absorption and distribution

Following oral administration, candesartan cilexetil is converted to the active substance candesartan. The absolute bioavailability of candesartan is approximately 40% after an oral solution of candesartan cilexetil. The relative bioavailability of the capsule formulation compared with the same oral solution is approximately 34% with very little variability. The estimated absolute bioavailability of the capsule is therefore 14%. The mean peak serum concentration (C_{max}) is reached 3-4 hours following capsule 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 and elimination

Candesartan is mainly eliminated unchanged via urine and bile and only to a minor extent eliminated by hepatic metabolism (CYP2C9). Available interaction studies indicate no effect on CYP2C9 and

CYP3A4. Based on in vitro data, no interaction would be expected to occur in vivo with 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

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).

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

t_{1/2} of candesartan was approximately doubled in patients with severe renal impairment. The AUC of candesartan in patients undergoing haemodialysis was similar to that in patients with severe renal impairment. In 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.

Amlodipine

Absorption, distribution, plasma protein binding: 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.

Biotransformation/elimination

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.

Use in hepatic impairment

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%.

Use in the elderly

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.

5.3 Preclinical safety data

Preclinical data available for the components of this fixed dose combination are reported below.

Candesartan

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

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

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

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

There was no evidence of carcinogenicity.

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/m² 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/m² 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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content:

Lactose Monohydrate

Maize Starch

Carmellose Calcium

Macrogol Type 8000

Hydroxypropylcellulose / type: EXF (250-800 cps (for 10% solution))

Hydroxypropylcellulose / type: LF (65-175 cps (for 5% solution))

Magnesium stearate

Capsule shell (8 mg + 5 mg, 8 mg + 10 mg):

Quinoline yellow (E 104)

Iron oxide yellow (E 172)

Titanium dioxide (E 171)

Gelatin

Capsule shell (16 mg + 5 mg):
Quinoline yellow (E 104)
Titanium dioxide (E 171)
Gelatin

Capsule shell (16 mg + 10 mg):
Titanium dioxide (E 171)
Gelatin

Ink (8 mg + 10 mg, 16 mg + 5 mg):
Shellac (E904)
Iron Oxide Black (E172)
Propylene Glycol
Ammonia Solution, concentrated
Potassium Hydroxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

30 months.

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

PA/Aluminium/PVC/Aluminium foil in a carton box.
The pack contains 14, 28, 30, 56, 60, 90, 98, 100 capsules, hard.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

<[To be completed nationally]>

8. MARKETING AUTHORISATION NUMBER(S)

<[To be completed nationally]>

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

<[To be completed nationally]>

10. DATE OF REVISION OF THE TEXT

<[To be completed nationally]>