SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE HUMAN MEDICINAL PRODUCT

CANLOX PLUS 16 mg/5 mg/12.5 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains;
Active substances:
Candesartan cilexetil 16 mg
Amlodipine besylate 6.94 mg (equivalent to 5 mg amlodipine)
Hydrochlorothiazide 12.5 mg

Excipients with known effect:
Sodium starch glycolate 13.5 mg
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.
Round, biconvex, bilayer tablets, debossed with "16" on pink side, debossed with "5" on white to off-white side.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications
It is indicated for the treatment of essential hypertension.
This fixed-dose combination is indicated in patients whose blood pressure is not adequately controlled with candesartan, amlodipine alone or candesartan/amlodipine combination (see sections 4.3, 4.4, 4.5 and 5.1).

4.2. Posology and method of administration
Posology, frequency and duration of administration
CANLOX PLUS can be used once daily with or without meals in patients whose blood pressure is not adequately controlled with candesartan, amlodipine alone or candesartan/amlodipine combination (see sections 4.3, 4.4, 4.5 and 5.1).

The treatment dose of CANLOX PLUS is to be decided by the doctor. A higher or lower dose may be recommended according to treatment response.

Method of administration
CANLOX PLUS should be taken once daily with or without food.
The bioavailability of CANLOX PLUS is not affected by food.

Additional information on special populations
Renal impairment
Dose titration of candesartan cilexetil is recommended in patients with creatinine clearance ≥30 ml/min/1.73 m² BSA before treatment with CANLOX PLUS (the recommended starting dose of

candesartan cilexetil is 4 mg in these patients). Since this titration cannot be achieved with CANLOX PLUS, it should not be used in initial treatment of patients with mild to moderate renal impairment (creatinine clearance <30 ml/min/1.73 m² BSA.

Changes in amlodipine plasma concentration are not correlated with degree of renal impairment. Amlodipine is not dialyzable.

The treatment dose of CANLOX PLUS is to be decided by the doctor. A higher or lower dose may be recommended according to treatment response.

Hepatic impairment
The recommended initial dose of candesartan cilexetil in patients with mild to moderate hepatic impairment is 4 mg. Since this dose cannot be achieved with CANLOX PLUS, it should not be used in initial treatment of patients with mild to moderate hepatic impairment.

Dosage recommendations for amlodipine have not been established in patients with mild to moderate hepatic impairment; therefore, dose selection should be cautious and should start at the lower end of the dosing range (see sections 4.4 and 5.2).

The pharmacokinetics of amlodipine has not been studied in severe hepatic impairment. Amlodipine should be initiated at the lowest dose and titrated slowly in patients with severe hepatic impairment.

CANLOX PLUS is contraindicated in patients with severe hepatic impairment and/or cholestasis (see sections 4.3 and 5.2).

The treatment dose of CANLOX PLUS is to be decided by the doctor. A higher or lower dose may be recommended according to treatment response.

Geriatric population
No adjustment of the recommended dose is generally required for elderly people but increase of the dosage should take place with care (see sections 4.4 and 5.2). Blood pressure should be monitored more frequently. CANLOX PLUS should be used with caution in patients over 75 years of age.

Pediatric population
The safety and efficacy of CANLOX PLUS in children and adolescents (<18 years old) have not been established. It is not recommended to use in this age group.

Patients with intravascular volume depletion
An initial dose of 4 mg of candesartan may be considered in patients at risk for hypotension, such as patients with possible volume depletion (see section 4.4). Since this dose cannot be achieved with CANLOX PLUS, it should not be used in patients with intravascular volume depletion.

Black patients
The antihypertensive effect of candesartan is less pronounced in black patients than in non-black patients. Consequently, titration of CANLOX PLUS may be more frequently needed in black patients than in non-black patients (see section 5.1).

4.3. Contraindications
- Hypersensitivity to any of the ingredients of CANLOX PLUS, dihydropyridine or sulfonamide derivatives (hydrochlorothiazide is a sulfonamide derivative) (see section 6.1)

- Pregnancy and breast-feeding (see section 4.6)
- Severe renal impairment (creatinine clearance of <30 ml/min/1.73 m² BSA)
- Severe hepatic impairment and/or cholestasis
- Severe hypotension
- Shock (including cardiogenic shock)
- Obstruction of the outflow tract of the left ventricle (e.g. high grade aortic stenosis)
- Hemodynamically unstable heart failure after acute myocardial infarction
- Refractory hypokalemia and hypercalcemia
- Gout
- The concomitant use of angiotensin II receptor blockers (ARBs) or angiotensin converting enzyme (ACE) inhibitors 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).
- Anuria

4.4. Special warnings and precautions for use

Acute Respiratory Toxicity

Very rarely, serious cases of acute respiratory toxicity, including acute respiratory distress syndrome (ARDS), have been reported following hydrochlorothiazide ingestion. Pulmonary edema typically develops within minutes or hours after hydrochlorothiazide ingestion. Initial symptoms include dyspnea, fever, pulmonary deterioration, and hypotension. If ARDS is suspected, CANLOX PLUS treatment should be discontinued and appropriate treatment administered. Hydrochlorothiazide should not be administered to patients who have previously experienced ARDS following hydrochlorothiazide ingestion.

Renal impairment/kidney transplantation

Loop diuretics are preferred to thiazides in this population. When CANLOX PLUS is used in patients with impaired renal function, a periodic monitoring of potassium, creatinine and uric acid levels is recommended.

There is no experience regarding the administration of candesartan cilexetil / hydrochlorothiazide in patients with a recent kidney transplantation or end-stage kidney failure (creatinine clearance <15 ml/min).

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

Hemodialysis

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

Cardiac failure

Patients with heart failure should be treated with caution. In a long-term, placebo controlled study in patients with severe heart failure (New York Heart Association-NYHA class III and IV) the reported incidence of pulmonary edema 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 use with other ACE-inhibitors in heart failure
The risk of adverse reactions, especially hypotension, hyperkalemia and decreased renal function (including acute renal failure), may increase when CANLOX PLUS 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.

Hepatic impairment
Exposure to amlodipine is increased in hepatic failure. Thiazides should be used with caution in patients with hepatic failure or progressive liver disease, as minor changes in water and electrolyte balance may cause hepatic coma. There is no clinical experience with the use of candesartan cilexetil / amlodipine / hydrochlorothiazide in patients with hepatic impairment. CANLOX PLUS should be administered with caution in patients with mild to moderate hepatic impairment. Amlodipine should be started at the lowest dose and the dose should be increased carefully. It is contraindicated in severe hepatic impairment.

Renal artery stenosis
Medicinal products that affect the renin-angiotensin-aldosterone system, including ACE inhibitors, may increase blood urea and serum creatinine in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney. The same effect can be seen with angiotensin II receptor antagonists (AIIRA).

Intravascular volume depletion
In patients with intravascular volume and/or sodium depletion symptomatic hypotension may occur, as described for other agents acting on the renin-angiotensin-aldosterone system. Therefore, the use of CANLOX PLUS is not recommended until this condition has been corrected (The recommended initial dose of candesartan cilexetil is 4 mg in these patients).

Anesthesia and surgery
Hypotension may occur during anesthesia 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 or obstructive hypertrophic cardiomyopathy
As with other vasodilators, special caution is indicated in patients suffering from hemodynamically relevant aortic or mitral valve stenosis, or obstructive hypertrophic cardiomyopathy.

Primary hyperaldosteronism
Patients with primary hyperaldosteronism generally will not respond to antihypertensive medicines acting through inhibition of the renin-angiotensin-aldosterone system. Therefore, the use of CANLOX PLUS is not recommended in these patients.

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, hyperkalemia 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.

Electrolyte imbalance
Periodic determination of serum electrolytes should be performed at appropriate intervals. Thiazides, including hydrochlorothiazide, can cause fluid or electrolyte imbalance (hypercalcemia, hypokalemia, hyponatremia, hypomagnesemia and hypochloremic alkalosis). Findings pointing to fluid-electrolyte imbalance are dry mouth, thirst, weakness, fatigue, drowsiness, muscle aches or cramps, muscle weakness, hypotension, oliguria, tachycardia, arrhythmia or gastrointestinal disturbances such as nausea, vomiting.

Thiazide diuretics may decrease the urinary calcium excretion and may cause intermittent and slightly increased serum calcium concentrations.

Marked hypercalcemia may be a sign of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Hydrochlorothiazide dose-dependently increases urinary potassium excretion which may result in hypokalemia. This effect of hydrochlorothiazide seems to be less evident when combined with candesartan cilexetil. The risk for hypokalemia may be increased in patients with cirrhosis of the liver, in patients experiencing brisk diuresis, in patients with an inadequate oral intake of electrolytes and in patients receiving concomitant therapy with corticosteroids or adrenocorticotropic hormone (ACTH).

Treatment with candesartan cilexetil may cause hyperkalemia, especially in the presence of heart failure and/or renal impairment. Concomitant use of CANLOX PLUS potassium-sparing diuretics, potassium supplements or salt substitutes or other medicinal products that may increase serum potassium levels (e.g. heparin sodium) may lead to increases in serum potassium. Monitoring of potassium should be undertaken as appropriate.

Thiazides have been shown to increase the urinary excretion of magnesium, which may result in hypomagnesaemia.

Metabolic and endocrine effects
Treatment with a thiazide diuretic may impair glucose tolerance. Dose adjustment of antidiabetic medicinal products, including insulin, may be required. Latent diabetes mellitus may become manifest during thiazide therapy. Increases in cholesterol and triglyceride levels have been associated with thiazide diuretic therapy. Thiazide diuretics increase serum uric acid concentration and may precipitate gout in susceptible patients.

Photosensitivity
Cases of photosensitivity reactions have been reported during use of thiazide diuretics (see section 4.8). If a photosensitivity reaction occurs, it is recommended to stop treatment. If re-administration of treatment is essential, it is recommended to protect areas exposed to the sun or to artificial UVA radiation.

General
In patients whose vascular tone and renal function depend predominantly on the activity of the renin-angiotensin-aldosterone system (e.g. patients with severe congestive heart failure or renal diseases, including renal artery stenosis), treatment with the other medicinal products that affect this system, has been associated with acute hypotension, azotemia, oliguria or, rarely, acute renal failure. The possibility of similar effects to AIIRA cannot be excluded. As with any antihypertensive agent, excessive blood pressure decrease in patients with ischemic heart disease or atherosclerotic cerebrovascular disease could result in a myocardial infarction or stroke.

Hypersensitivity reactions to hydrochlorothiazide may occur in patients with or without a history of allergy or bronchial asthma, but are more likely in patients with such a history.

Exacerbation or activation of systemic lupus erythematosus may occur with the use of thiazide diuretics.

The antihypertensive effect of CANLOX PLUS may be enhanced by other antihypertensives given as antihypertensive or for other indications.

The antihypertensive effect of candesartan is less in black patients than in non-black patients. Consequently, black patients may require more frequent titration of CANLOX PLUS and combined therapy than non-black patients (see section 5.1).

The vasodilator effect of amlodipine begins gradually. Therefore, rare cases of acute hypotension have been reported after oral administration of amlodipine. CANLOX PLUS should be used with caution, like other peripheral vasodilators, especially in patients with severe aortic stenosis.

Non-melanoma skin cancer
An increased risk of non-melanoma skin cancer (basal cell carcinoma and squamous cell carcinoma) with increasing cumulative dose of hydrochlorothiazide exposure has been observed in two epidemiological studies based on the Danish National Cancer Registry. Photosensitizing actions of hydrochlorothiazide could act as a possible mechanism for non-melanoma skin cancer.

Patients taking hydrochlorothiazide should be informed of the risk of non-melanoma skin cancer and advised to regularly check their skin for any new lesions and promptly report any suspicious skin lesions. Possible preventive measures such as limited exposure to sunlight and UV rays and, in case of exposure, adequate protection should be advised to the patients in order to minimize the risk of skin cancer. Suspicious skin lesions should be promptly examined potentially including histological examinations of biopsies. The use of hydrochlorothiazide may also need to be reconsidered in patients who have experienced previous non-melanoma skin cancer (see section 4.8).

Pregnancy
CANLOX PLUS therapy should not be initiated during pregnancy. Unless continued CANLOX 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 CANLOX should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

In menstruating patients the possibility of pregnancy should be evaluated on a regular basis. Appropriate information should be given and/or action taken to prevent the risk of exposure during

pregnancy (see sections 4.3 and 4.6).

Intestinal angioedema:
Intestinal angioedema has been reported in patients treated with angiotensin II receptor blockers [including CANLOX PLUS] (see Section 4.8). These patients have experienced abdominal pain, nausea, vomiting, and diarrhea. Symptoms resolved after discontinuation of the angiotensin II receptor blocker. If intestinal angioedema is diagnosed, CANLOX PLUS treatment should be stopped and appropriate monitoring should be initiated until symptoms fully resolve.

This medicine contains less than 1 mmol (23 mg) of sodium per tablet, meaning it is essentially "sodium-free".

4.5. Interactions with other medicinal products and other forms of interaction
Compounds which have been investigated with candesartan cilexetil 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.
The potassium depleting effect of hydrochlorothiazide could be expected to be potentiated by other medicinal products associated with potassium loss and hypokalemia (e.g. other kaliuretic diuretics, laxatives, amphotericin, carbenoxolone, penicillin G sodium, salicylic acid derivates, steroids, ACTH).

Concomitant use of CANLOX PLUS and potassium-sparing diuretics, potassium supplements, salt substitute, or other medicinal products may increase potassium levels (e.g. heparin sodium) may lead to increases in serum potassium.). Monitoring of potassium should be undertaken as appropriate (see section 4.4).

Dual blockade of the renin-angiotensin-aldosterone system (RAAS) through the combined use of AII receptor antagonists, ACE inhibitors or aliskiren
Clinical data have shown that dual blockade of the renin-angiotensin-aldosterone system (RAAS) through the combined use of ACE inhibitors, AIIRAs or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalemia 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).

Diuretic-induced hypokalemia and hypomagnesemia predisposes to the potential cardiotoxic effects of digitalis glycosides and antiarrhythmics. Periodic monitoring of serum potassium is recommended when CANLOX PLUS is administered with such medicinal products, and with the following medicinal products that could induce torsades de pointes:
- Class Ia antiarrhythmics (e.g. quinidine, hydroquinidine, disopyramide)
- Class III antiarrhythmics (e.g. amiodarone, sotalol, dofetilide, ibutilide)
- Some antipsychotics (e.g. thioridazine, chlorpromazine, levomepromazine, trifluoperazine, cyamemazine, sulpiride, sultopride, amisulpride, tiapride, pimozide, haloperidol, droperiodol)
- Others (e.g. bepridil, cisapride, diphemanil, erythromycin iv, halofantrin, ketanserin, mizolastin, pentamidine, sparfloxacine, terfenadine, vincamine iv)

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors or hydrochlorothiazide. A similar effect may also be observed with AIIRAs. Use of candesartan and hydrochlorothiazide with lithium is not

recommended. If the combination is necessary, careful monitoring of serum lithium levels is recommended.

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

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.

The diuretic, natriuretic and antihypertensive effect of hydrochlorothiazide is blunted by NSAIDs.

The absorption of hydrochlorothiazide is reduced by colestipol or cholestyramine.

The effect of nondepolarising skeletal muscle relaxants (e.g. tubocurarine) may be potentiated by hydrochlorothiazide.

Thiazide diuretics may increase serum calcium levels due to decreased excretion. If calcium supplements or Vitamin D must be prescribed, serum calcium levels should be monitored and the dose adjusted accordingly.

The hyperglycemic effect of beta-blockers and diazoxide may be enhanced by thiazides.

Anticholinergic agents (e.g. atropine, biperiden) may increase the bioavailability of thiazide-type diuretics by decreasing gastrointestinal motility and stomach emptying rate.

Thiazide may increase the risk of adverse effects caused by amantadine.

Thiazides may reduce the renal excretion of cytotoxic medicinal products (e.g. cyclophosphamide, methotrexate) and potentiate their myelosuppressive effects.

Because hydrochlorothiazide may increase serum uric acid levels, it may be necessary to adjust the dosage of uricosuric drugs used in the treatment of gout (e.g., probenecid, sulfinpyrazone, allopurinol). The dose of probenecid or sulfinpyrazone may be increased. Co-administration with thiazide may increase the incidence of hypersensitivity reactions to allopurinol.

It may reduce the absorption of tetracyclines due to its magnesium content. Therefore, simultaneous use is not recommended.

Postural hypotension may become aggravated by simultaneous intake of alcohol, barbiturates or anesthetics.

Treatment with a thiazide diuretic may impair glucose tolerance. Dose adjustment of antidiabetic medicinal products, including insulin, may be required. Metformin should be used with caution because of the risk of lactic acidosis induced by possible functional renal failure linked to

hydrochlorothiazide.

Hydrochlorothiazide may cause the arterial response to pressor amines (e.g. adrenaline) to decrease but not enough to exclude a pressor effect.

Hydrochlorothiazide may increase the risk of acute renal insufficiency especially with high doses of iodinated contrast media.

Concomitant treatment with cyclosporine may increase the risk of hyperuricemia and gout-type complications.

Concomitant treatment with baclofen, amifostin, tricyclic antidepressants or neuroleptics may lead to enhancement of the antihypertensive effect and may induce hypotension.

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 pharmacokinetic variations may be more pronounced in the elderly. Clinical monitoring 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).

Grapefruit juice
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 coadministration 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.

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.

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

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.

Additional information on special populations
Pediatric population
Interaction studies were performed only in adults.

4.6. Fertility, pregnancy and lactation
General recommendation
Pregnancy category is “D”.

Women of child-bearing potential/Contraception
Women of child-bearing potential who use CANLOX PLUS have to use effective contraception during treatment.

Pregnancy
CANLOX PLUS has harmful pharmacological effects on pregnancy and/or fetus/newborn.

CANLOX PLUS is contraindicated during pregnancy.

Patients using CANLOX PLUS should be reminded of the possibility of pregnancy before they can determine the appropriate option with their attending physician. If pregnancy is detected, treatment with CANLOX PLUS should be stopped immediately and, where appropriate, alternative treatment initiated.

Medicinal products with a direct effect on the renin-angiotensin system can cause fetal and neonatal damage or even death when used during pregnancy. Exposure to therapy with angiotensin II receptor antagonist therapy during pregnancy is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalemia) (see section 5.3).

There is limited experience with hydrochlorothiazide during pregnancy, especially during the first trimester. Animal studies are insufficient. Hydrochlorothiazide crosses the placenta. Based on the pharmacological mechanism of action of hydrochlorothiazide its use during the second and third

trimesters may compromise feto-placental perfusion and may cause fetal and neonatal effects like icterus, disturbance of electrolyte balance and thrombocytopenia.

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).

Experience with the use of hydrochlorothiazide during pregnancy, particularly in the first trimester, is limited. Animal studies are insufficient. Hydrochlorothiazide crosses the placenta. Based on its pharmacological mechanism of action, its use during pregnancy may compromise fetoplacental perfusion and cause fetal or neonatal effects such as jaundice, electrolyte imbalance, and thrombocytopenia.

Breast-feeding
It is not known whether candesartan passes into breast milk. Hydrochlorothiazide passes in low amounts. Excretion of candesartan has been observed in lactating rats. Breastfeeding should be discontinued when use of CANLOX PLUS is necessary due to the potential for adverse effects in infants who are breastfed (see section 4.3).

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.

Reproductive ability / Fertility
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. Amlodipine can have minor or moderate influence on the ability to drive and use machines. If patients taking CANLOX PLUS 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
In controlled clinical studies adverse reactions were mild and transient. Withdrawals from treatment due to adverse events were similar with candesartan cilexetil (3.3%) and placebo (2.7%).

In clinical trials with candesartan cilexetil/hydrochlorothiazide, adverse reactions were limited to those that were reported previously with candesartan cilexetil and/or hydrochlorothiazide

Adverse reactions with candesartan cilexetil from clinical trials and postmarketing experience are presented below. In a pooled analysis of clinical trial data of hypertensive patients, adverse reactions with candesartan cilexetil were at least 1% higher than the incidence seen with placebo.

The frequencies used throughout this section are; very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000) and not known

(cannot be estimated from the available data).

Candesartan
Infections and infestations
Common: Respiratory tract infections

Blood and lymphatic system disorders
Very rare: Leucopenia, neutropenia and agranulocytosis

Metabolism and nutrition disorders
Very rare: Hyperkalemia, hyponatremia

Nervous system disorders
Common: Dizziness/vertigo, headache

Respiratory, thoracic and mediastinal disorders
Very rare: Cough

Gastrointestinal disorders
Very rare: Nausea, intestinal angioedema

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 system disorders, connective tissue and bone disorders
Very rare: Back pain, arthralgia, myalgia

Renal and urinary disorders
Very rare: Renal impairment, including renal failure in susceptible patients (creatinine clearance <15 ml/min) (see section 4.4)

Laboratory findings
In general, there are no clinically important influences of CANLOX PLUS on routine laboratory variables. As for other inhibitors of the renin-angiotensin-aldosterone system, small decreases in hemoglobin have been observed. No routine monitoring of laboratory variables is usually necessary for patients receiving CANLOX PLUS. However, in patients with renal impairment, periodic monitoring of serum potassium and creatinine levels is recommended.

Hydrochlorothiazide
The following adverse reactions have been reported with hydrochlorothiazide monotherapy usually with doses of 25 mg or higher

Blood and lymphatic system disorders
Rare: Leukopenia, neutropenia/agranulocytosis, thrombocytopenia, aplastic anemia, bone marrow depression, hemolytic anemia

Immune system disorders

Rare: Anaphylactic reactions

Metabolism and nutrition disorders
Common: Hyperglycemia, hyperuricemia, electrolyte imbalance (including hyponatremia and hypokalemia)

Psychiatric disorders
Rare: Sleep disturbances, depression, restlessness

Nervous system disorders
Common**:** Light-headedness, vertigo
Rare: Paresthesia

Eye disorders
Rare: Transient blurred vision
Not known: Acute myopia, acute angle-closure glaucoma

Cardiac disorders
Rare: Cardiac arrhythmias

Vascular disorders
Uncommon: Postural hypotension
Rare: Necrotizing angiitis (vasculitis, cutaneous vasculitis)

Respiratory, thoracic and mediastinal disorders
Rare: Respiratory distress (including pneumonitis and pulmonary edema)
Very rare: Acute respiratory distress syndrome (ARDS) (see Section 4.4)

Gastrointestinal disorders
Uncommon: Anorexia, loss of appetite, gastric irritation, diarrhea, constipation
Rare: Pancreatitis

Hepatobiliary disorders
Rare: Jaundice (intrahepatic cholestatic jaundice)

Skin and subcutaneous tissue disorders
Uncommon: Rash, urticaria, photosensitivity reactions
Rare: Toxic epidermal necrolysis, cutaneous lupus erythematosus-like reactions, reactivation of cutaneous lupus erythematosus

Musculoskeletal and connective tissue disorders
Rare: Muscle spasm

Neoplasms benign, malignant and unspecified (incl cysts and polyps)
Not known: Non-melanoma skin cancer (Basal cell carcinoma and squamous cell carcinoma)

Renal and urinary disorders
Common: Glycosuria
Rare: Renal dysfunction and interstitial nephritis

General disorders and administration site conditions
Common: Weakness
Rare: Fever

Investigations
Common: Increases in cholesterol and triglycerides
Rare: Increases in BUN and serum creatinine

Description of selected adverse reactions
Non-melanoma skin cancer: Based on available data from epidemiological studies, cumulative dose-dependent association between hydrochlorothiazide and non-melanoma skin cancer has been observed (see sections 4.4 and 5.1).

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, edema and fatigue.

The list of adverse reactions
The adverse reactions presented below have been observed 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) and not known (cannot be estimated from the available data).

Blood and the lymphatic system disorders
Very rare: Thrombocytopenia, leucopenia
Immune system disorders
Very rare: Allergic reaction

Metabolism and nutrition disorders
Very rare: Hyperglycemia

Psychiatric disorders
Uncommon: Sleeplessness (insomnia), mood changes (including anxiety), depression, irritability
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

Eye disorders
Common: Visual disturbance (including diplopia and blurred vision)

Ear and labyrinth disorders
Uncommon: Tinnitus

Cardiac disorders
Common: Palpitation
Uncommon: Arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation)
Very rare: Myocardial infarction

Vascular disorders
Common: Flushing
Uncommon: Hypotension
Very rare: Vasculitis (including necrotizing angiitis)

Respiratory, thoracic and mediastinal disorders
Common: Dyspnea
Uncommon: Cough, rhinitis

Gastrointestinal disorders
Common: Abdominal pain, nausea, dyspepsia, altered bowel habits (including diarrhea and constipation)
Uncommon: Vomiting, dry mouth
Very rare: Gingival hyperplasia, pancreatitis, gastritis

Hepatobiliary disorders
Very rare: Hepatitis, jaundice, raised hepatic enzymes (mostly consistent with cholestasis)

Skin and subcutaneous tissue disorders
Uncommon: Alopecia, purpura, hyperhydrosis, itching (pruritus), skin discoloration, rash, exanthema
Very rare: Angioedema, erythema multiforme, urticaria, exfoliative dermatitis, Stevens-Johnson syndrome, Quincke edema, photosensitivity
Unknown: Toxic epidermal necrosis
Musculoskeletal, connective tissue and bone disorders
Common: Ankle swelling, muscle cramps
Uncommon: Arthralgia, myalgia, back pain

Renal and urinary disorders
Uncommon: Increased urinary frequency, micturition disorder, nocturia

Reproductive system and breast disorders
Uncommon: Impotence, gynecomasty

General disorders and administration site conditions
Very common: Edema
Common: Fatigue, asthenia
Uncommon: Chest pain, malaise, pain

Investigations
Uncommon: Weight increase/decrease

Exceptional cases of extrapyramidal syndrome have been observed.

Reporting of side effects
If you get any side effects including any possible side effects not listed in this leaflet, talk to your doctor, pharmacist or nurse. You can also report side effects directly in accordance with local requirements.

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

The main manifestation of an overdose of hydrochlorothiazide is acute loss of fluid and electrolytes. Symptoms such as dizziness, hypotension, thirst, tachycardia, ventricular arrhythmias, sedation/impairment of consciousness and muscle cramps can also be observed.

No specific information is available on the treatment of overdosage with CANLOX PLUS. The following measures are, however, suggested in case of overdosage.

When indicated, induction of vomiting or gastric lavage should be considered.
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 isotonic saline solution. Serum electrolyte and acid balance should be checked and corrected, if needed. Sympathomimetic medicinal products may be administered if the above-mentioned measures are not sufficient.

Candesartan cannot be removed by hemodialysis. It is not known to what extent hydrochlorothiazide is removed by hemodialysis.

Amlodipine
Symptoms:
In humans experience with intentional overdose is limited.
Available data suggest that gross overdosage 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.

Treatment:
Clinically significant hypotension due to amlodipine over dosage 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. Administration of activated charcoal to healthy volunteers immediately or up to two hours after ingestion of amlodipine 10 mg has been shown to significantly decrease amlodipine absorption.

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

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties
Pharmacotherapeutic group: Angiotensin II receptor blockers (ARBs), other combinations
ATC code: C09DX06

Candesartan
Angiotensin II is the primary vasoactive hormone of the renin-angiotensin-aldosterone system and plays a role in the pathophysiology of hypertension and other cardiovascular disorders. It also has an important role in the pathogenesis of organ hypertrophy and end organ 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 which is rapidly converted to the active drug, 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 influence ACE or other enzyme systems usually associated with the use of ACE inhibitors. Since there is no effect on the degradation of kinins, or on the metabolism of other substances, such as substance P, AIIRAs are unlikely to be associated with cough. In controlled clinical trials comparing candesartan cilexetil with ACE inhibitors, the incidence of cough was lower in patients receiving candesartan cilexetil. Candesartan does not bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation. The antagonism of the Angiotensin II (AT1) receptors results in dose related increases in plasma renin levels, angiotensin I and angiotensin II levels, and a decrease in plasma aldosterone concentration.

Hypertension
In hypertension, candesartan causes a dose-dependent, long-lasting reduction in arterial blood pressure. The antihypertensive action is due to decreased systemic peripheral resistance, without reflex increase in heart rate. There is no indication of serious or exaggerated first dose hypotension or rebound effect after cessation of treatment.

After administration of a single dose of candesartan cilexetil, onset of antihypertensive effect generally occurs within 2 hours. With continuous treatment, most of the reduction in blood pressure with any dose is generally attained within four weeks and is sustained during long-term treatment. According to the 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 randomized, 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 10/8.7 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. Candesartan was well tolerated when co-administered with hydrochlorothiazide or amlodipine.

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 19/12.7 mmHg, p<0.0001/p<0.0001).

Candesartan increases renal blood flow and either has no effect on or increases glomerular filtration rate while renal vascular resistance and filtration fraction are reduced. In a 3-month clinical study in hypertensive patients with type 2 diabetes mellitus and microalbuminuria, antihypertensive treatment with candesartan cilexetil reduced urinary albumin excretion (albumin/creatinine ratio, mean 30%, 95% confidence interval 15-42%). There is currently no data on the effect of candesartan on the progression to diabetic nephropathy.

The effects of candesartan cilexetil 8-16 mg (mean dose 12 mg), once daily, on cardiovascular morbidity and mortality were evaluated in a randomized 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 (SCOPE - 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 events per 1000 patient-years in the control group (relative risk 0.89, 95% confidence interval 0.75 to 1.06, p=0.19).

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

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

These studies have shown no significant beneficial effect on renal and/or cardiovascular outcomes and mortality, while an increased risk of hyperkalemia, 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 AIIRA 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 (hyperkalemia, hypotension and renal dysfunction) were more frequently reported in the aliskiren group than in the placebo group.

Hydrochlorothiazide

Hydrochlorothiazide inhibits the active reabsorption of sodium, mainly in the distal kidney tubules, and promotes the excretion of sodium, chloride and water. The renal excretion of potassium and magnesium increases dose-dependently, while calcium is reabsorbed to a greater extent. Hydrochlorothiazide decreases plasma volume and extracellular fluid and reduces cardiac output and blood pressure. During long-term therapy, reduced peripheral resistance contributes to the blood pressure reduction.

Large clinical studies have shown that long-term treatment with hydrochlorothiazide reduces the risk for cardiovascular morbidity and mortality.

When candesartan is used in combination hydrochlorothiazide, amlodipine or felodipine, they demonstrate additive antihypertensive effect.

In hypertensive patients, candesartan cilexetil/hydrochlorothiazide results in an effective and long-lasting reduction in arterial blood pressure 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, onset of the antihypertensive effect generally occurs within 2 hours. With continuous treatment, most of the reduction in blood pressure is attained within four weeks and is sustained during long-term treatment. Candesartan cilexetil/hydrochlorothiazide once daily provides effective and smooth blood pressure reduction over 24 hours, with little difference between maximum and trough effects during the dosing interval.

In a double-blind randomized study, candesartan cilexetil/hydrochlorothiazide once daily reduced blood pressure significantly more, and controlled significantly more patients, than other combinations of AIIRA and hydrochlorothiazide. In double-blind, randomized studies, the incidence of adverse events, especially cough, was lower during treatment with candesartan cilexetil/hydrochlorothiazide than during treatment with combinations of ACE inhibitors and hydrochlorothiazide.

Non-melanoma skin cancer: Based on available data from epidemiological studies, cumulative dose-dependent association between hydrochlorothiazide and non-melanoma skin cancer has been observed. One study included a population comprised of 71,533 cases of basal cell carcinoma and of 8,629 cases of squamous cell carcinoma matched to 1,430,833 and 172,462 population controls, respectively. High hydrochlorothiazide use (≥50,000 mg cumulative) was associated with an adjusted odds ratio (OR) of 1.29 (95% confidence interval (CI): 1.23-1.35) for basal cell carcinoma and 3.98 (95% CI: 3.68-4.31) for squamous cell carcinoma. A clear cumulative dose response relationship was observed for both basal cell carcinoma and squamous cell carcinoma. Another study showed a possible association between lip cancer and exposure to hydrochlorothiazide: 633 cases of lip-cancer were matched with 63,067 population controls, using a risk-set sampling strategy. A cumulative dose-response relationship was demonstrated with an adjusted OR 2.1 (95% CI: 1.7-2.6) increasing to OR 3.9 (3.0-4.9) for high use (~25,000 mg) and OR 7.7 (5.7-10.5) for the highest cumulative dose (~100,000 mg) (see section 4.4).

In two randomized, double-blind, placebo-controlled clinical studies of candesartan cilexetil/hydrochlorothiazide combinations, in which 275 patients were randomized to placebo and 1524 patients to the 32 mg/12.5 mg and 32 mg/25 mg groups; the candesartan cilexetil/hydrochlorothiazide combinations 32 mg/12.5 mg and 32 mg/25 mg resulted in blood pressure reductions of 22/15 mmHg and 21/14 mmHg, respectively, and were significantly more effective than the respective mono components.

In a randomized, double-blind, parallel group clinical study including 1,975 randomized patients not

optimally controlled on 32 mg candesartan cilexetil once daily, the addition of 12.5 mg or 25 mg hydrochlorothiazide resulted in additional blood pressure reductions. The candesartan cilexetil/hydrochlorothiazide combination 32 mg/25 mg was significantly more effective than the 32 mg/12.5 mg combination and the overall mean blood pressure reductions were 16/10 mmHg and 13/9 mmHg, respectively.

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

Currently there are no data on the use of candesartan cilexetil/hydrochlorothiazide in patients with renal disease/nephropathy, reduced left ventricular function/congestive heart failure and post myocardial infarction.

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 ischemic 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 ischemic 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.

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.

The effectiveness of amlodipine in preventing clinical events in patients with coronary artery disease (CAD) has been evaluated in an independent, multi-centre, randomized, double-blind, placebo-controlled study of 1997 patients; Comparison of Amlodipine vs. Enalapril to Limit Occurrences of Thrombosis (CAMELOT). Of these patients, 663 were treated with amlodipine 5-10 mg and 655 patients were treated with placebo, in addition to standard care of statins, beta-blockers, diuretics and aspirin, for 2 years. The key efficacy results are presented in Table 1. The results indicate that amlodipine treatment was associated with fewer hospitalizations for angina and revascularization procedures in patients with CAD.

Table 1. Incidence of Significant Clinical Outcomes for CAMELOT					
	Cardiovascular event rates No. (%)			Amlodipine vs. placebo	
Clinical Outcomes	Amlodipine	Placebo	Enalapril	Hazard Ratio (95% Confidence Interval -CI)	*P* value
Primary Endpoint					
Adverse cardiovascular events	110 (16.6)	151 (23.1)	136 (20.2)	0.69 (0.54 - 0.88)	0.003
Individual Components					
Coronary revascularization	78 (11.8)	103 (15.7)	95 (14.1)	0.73 (0.54 - 0.98)	0.03
Hospitalization for angina	51 (7.7)	84 (12.8)	86 (12.8)	0.58 (0.41 - 0.82)	0.002
Nonfatal myocardial infarction	14 (2.1)	19 (2.9)	11 (1.6)	0.73 (0.37 - 1.46)	0.37
Stroke or transient ischemic attack	6 (0.9)	12 (1.8)	8 (1.2)	0.5 (0.19 - 1.32)	0.15
Cardiovascular death	5 (0.8)	2 (0.3)	5 (0.7)	2.46 (0.48 - 12.7)	0.27
Hospitalization for congestive heart failure	3 (0.5)	5 (0.8)	4 (0.6)	0.59 (0.14 - 2.47)	0.46
Resuscitated cardiac arrest	0	4 (0.6)	1 (0.1)	NA	0.04
New-onset peripheral vascular disease	5 (0.8)	2 (0.3)	8 (1.2)	2.6 (0.5- 13.4)	0.24

Use in Patients with Heart Failure

Hemodynamic 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 angiotensin converting enzyme (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 long-term, placebo-controlled follow-up study (PRAISE - 2) in patients with NYHA III and IV heart failure of non-ischemic etiology and using stable doses of ACE inhibitors, digitalis and diuretics; amlodipine had no effect on total or cardiovascular mortality. In the same population, there was an increase in reports of pulmonary edema with the use of amlodipine, but there was no significant difference in the incidence of worsening heart failure compared to placebo.

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) and lisinopril 10-40 mg/d (angiotensin-converting-enzyme inhibitor (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 myocardial infarction or stroke >6 months 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 and 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 [0.9-1.07] 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=0.2.

The long-term effects of amlodipine on growth, puberty and general development have not been studied. The long-term efficacy of amlodipine on therapy in childhood to reduce cardiovascular morbidity and mortality in adulthood have also not been established.

5.2. Pharmacokinetic properties

General properties

Combined administration of candesartan cilexetil / amlodipine besylate / hydrochlorothiazide has no clinically significant effect on the pharmacokinetics of either medicinal product.

Absorption

Candesartan cilexetil

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 a tablet formulation of candesartan cilexetil compared with the same oral solution is approximately 34% with very little variability. Therefore, the estimated absolute bioavailability is 18%. 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. The bioavailability is not affected by food.

Hydrochlorothiazide

Hydrochlorothiazide is rapidly absorbed from the gastrointestinal tract with an absolute bioavailability of approximately 70%. Concomitant intake of food increases the absorption by approximately 15%. The bioavailability may decrease in patients with cardiac failure and pronounced edema.

Amlodipine besylate

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 bioavailability of amlodipine is not affected by food intake.

Distribution

Candesartan cilexetil

Candesartan is highly bound to plasma proteins (more than 99%). The apparent volume of distribution of candesartan is 0.1 l/kg.

Hydrochlorothiazide

The plasma protein binding of hydrochlorothiazide is approximately 60%. The apparent volume of distribution is approximately 0.8 l/kg.

Amlodipine besylate

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.

Biotransformation

Candesartan cilexetil

Available interaction studies indicate no effect on CYP2C9 and CYP3A4. Based on *in vitro* data, no interaction would be expected to occur *in vivo* between candesartan and medicinal product whose metabolism is dependent upon cytochrome P450 isoenzymes CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1 or CYP3A4. The terminal half-life ($t_{1/2}$) of candesartan is approximately 9 hours. It does not accumulate after repeated doses. When candesartan cilexetil is co-administered with hydrochlorothiazide, the $t_{1/2}$ of candesartan is unchanged (approximately 9 hours). No additional accumulation of candesartan occurs after repeated doses of the combination compared to monotherapy.

Hydrochlorothiazide

Hydrochlorothiazide is not metabolized and is excreted almost entirely as unchanged drug by glomerular filtration and active tubular secretion. The terminal $t_{1/2}$ of hydrochlorothiazide is approximately 8 hours. Approximately 70% of an oral dose is eliminated in the urine within 48 hours. The half-life of hydrochlorothiazide remains unchanged (approximately 8 h) after administration of hydrochlorothiazide in combination with candesartan cilexetil. No additional accumulation of hydrochlorothiazide occurs after repeated doses of the combination compared to monotherapy.

Amlodipine besylate

Steady state plasma levels are reached after 7-8 days of consecutive dosing. Amlodipine is extensively metabolized by the liver to inactive metabolites with 10% of the parent compound and 60% of metabolites excreted in the urine.

Elimination

Candesartan cilexetil

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

Total plasma clearance of candesartan is about 0.37 ml/min/kg, with a renal clearance of about 0.19 ml/min/kg. The renal elimination of candesartan is both by glomerular filtration and active tubular secretion. Following an oral dose of ^{14}C-labelled candesartan cilexetil, approximately 26% of the dose is excreted in the urine as candesartan and 7% as an inactive metabolite while approximately 56% of the dose is recovered in the feces as candesartan and 10% as the inactive metabolite.

Hydrochlorothiazide

The mean plasma half-life of hydrochlorothiazide has been reported in the range of 5-15 hours. Hydrochlorothiazide is rapidly excreted by the kidney without being metabolized. At least 61% of an oral dose is excreted unchanged within 24 hours. Hydrochlorothiazide crosses the placenta but does not cross the blood-brain barrier and is found in breast milk.

Amlodipine besylate

The terminal plasma elimination half life is about 35-50 hours and is consistent with once daily dosing.

Pharmacokinetics in special populations

Candesartan cilexetil

In elderly subjects (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 the terminal $t_{1/2}$ 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 pharmacokinetics in patients undergoing hemodialysis were similar to those 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. There was an approximately 23% increase in candesartan AUC in patients with mild to moderate hepatic impairment.

Hydrochlorothiazide
The terminal $t_{1/2}$ of hydrochlorothiazide is prolonged in patients with renal impairment.

Amlodipine besylate
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 area under the curve (AUC) and elimination half-life in patients with congestive heart failure were as expected for the patient age group studied.

Patients with impaired hepatic function
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%.

Patients with renal impairment
Amlodipine may be used in such patients at normal doses. Changes in amlodipine plasma concentrations are not correlated with degree of renal impairment, therefore the normal dosage is recommended. Amlodipine is not dialyzable.

Use in pediatric patients:
A population pharmacokinetic study has been conducted in 74 hypertensive children aged from 1 year to 17 years (with 34 patients aged 6 to 12 years and 28 patients aged 13 to 17 years) receiving amlodipine between 1.25 and 20 mg given either once or twice daily. In children 6 to 12 years and in adolescents 13-17 years of age, the typical oral clearance (CL/F) was 22.5 and 27.4 l/hr respectively in males and 16.4 and 21.3 l/hr respectively in females. Large variability in exposure between individuals was observed. Data reported in children below 6 years is limited.

5.3. Preclinical safety data
Candesartan and hydrochlorothiazide
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, hemoglobin, hematocrit). Animal studies with candesartan cilexetil show late fetal and neonatal damage to the kidney. The mechanism is thought to be mediated by a pharmacological action on the renin-angiotensin-aldosterone system. Renal effects (such as interstitial nephritis, tubular dysfunction, basophilic tubule, increased plasma urea and creatinine levels) may occur secondary to the hypotensive effect of candesartan leading to impaired renal perfusion. Addition of hydrochlorothiazide potentiates the nephrotoxicity of candesartan. Furthermore, candesartan induced hyperplasia/hypertrophy of the juxtaglomerular cells. These changes were considered to be caused by the pharmacological action of candesartan.

Fetotoxicity has been observed in late pregnancy with candesartan. The addition of hydrochlorothiazide did not significantly affect the outcome of fetal development studies in rats, mice or rabbits (see section 4.6).

Candesartan and hydrochlorothiazide both show genotoxic activity at very high concentrations/doses. Data from *in vitro* and *in vivo* genotoxicity testing indicate that candesartan and hydrochlorothiazide are unlikely to exert any mutagenic or clastogenic activity under conditions of clinical use.

There was no evidence that either compound is carcinogenic.

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

Carcinogenesis
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

Mutagenesis
Mutagenicity studies revealed no drug related effects at either the gene or chromosome level.

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 besylate 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.

*Based on patient weight of 50 kg.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients
Maize starch
Microcrystalline cellulose (Type 102)
Microcrystalline cellulose (Type 112)

Mannitol
Copovidone
Sodium starch glycolate
Calcium hydrogen phosphate
Red iron oxide
Glycerin
Colloidal silicon dioxide
Magnesium stearate

6.2. Incompatibilities
Not applicable.

6.3. Shelf life
24 months.

6.4. Special precautions for storage
Store at room temperature below 25°C in its package.

6.5. Nature and contents of packaging
Primary packaging is blisters of PA/ALU/PVC Foil/Aluminum foil.
Each cardboard box contains 28 tablets within blisters and package leaflet.

6.6 Special precautions for disposal and other handling
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORIZATION HOLDER

DEVA Holding A.Ş.
Halkalı Merkez Mah. Basın Ekspres Cad. No:1
34303 Küçükçekmece – Istanbul/TÜRKİYE

8. MARKETING AUTHORIZATION NUMBER

2019/420

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Date of first authorization: 18.08.2019
Date of last renewal:

10. DATE OF REVISION OF THE TEXT