SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

CANLOX 32 mg/10 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substances:
Candesartan cilexetil 32 mg
Amlodipine besylate 13.87 mg (equivalent to 10 mg amlodipine)

Excipients:
Sodium starch glycolate 15 mg
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.
Round, biconvex, bilayer tablets, debossed with "32" on pink side, debossed with "10" 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 or amlodipine monotherapy (see sections 4.3, 4.4, 4.5 and 5.1).

4.2 Posology and method of administration

Posology / frequency and duration of administration:
The recommended dose is 1 tablet daily. When clinically appropriate a direct change from monotherapy to the fixed combination may be considered. For convenience, patients receiving candesartan and amlodipine from separate tablets may switch to CANLOX containing the same component doses (see sections 4.3, 4.4, 4.5 and 5.1).

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

Method of administration:
CANLOX should be administered as a single dose daily. It can be taken on an empty or full stomach.
The bioavailability of CANLOX is not affected by food.

Additional information on special populations:
Renal impairment:
Dose titration of candesartan cilexetil is recommended in patients with mild to moderate renal impairment (creatinine clearance ≥30 ml/min/1.73 m² BSA) before treatment with CANLOX (The recommended starting dose of candesartan cilexetil in patients with mild to moderate renal impairment is 4 mg). Since this titration cannot be achieved with CANLOX, 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 dosage of CANLOX to be used depends on the physician's judgment. Depending on the response to treatment, the physician may recommend using a higher or lower dose.

Hepatic impairment:
The recommended initial dose of candesartan in patients with mild to moderate hepatic impairment is 4 mg. Since this dose cannot be achieved with CANLOX, 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 is contraindicated in patients with severe hepatic impairment and/or cholestasis (see sections 4.3 and 5.2).

The dosage of CANLOX to be used depends on the physician's judgment. Depending on the response to treatment, the physician may recommend using a higher or lower dose.

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

Pediatric population:
The safety and efficacy of CANLOX in children and adolescents (below 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 is recommended in patients at risk for hypotension, such as patients with possible intravascular volume depletion (see section 4.4). Since this dose cannot be achieved with CANLOX, 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 may be more frequently needed in black patients than in non-black patients (see section 5.1).

4.3 Contraindications
It is contraindicated in cases of
- Hypersensitivity to any of the excipients of CANLOX, or dihydropyridine derivatives (see section 6.1)
- Pregnancy and breast-feeding period (see section 4.6)

- Patients with 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 myocardial infarction
- The concomitant use of aliskiren with angiotensin II receptor blockers (ARBs) or angiotensin converting enzyme (ACE) inhibitors 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

Renal impairment:

As with other agents inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible patients treated with CANLOX.

When CANLOX 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 (creatinine clearance <15 ml/min). In these patients CANLOX should be carefully titrated with thorough monitoring of blood pressure.

Kidney function should be regularly assessed in the evaluation of heart failure patients, especially in patients over 75 years of age and those with renal failure. During dose titration of CANLOX, monitoring of serum creatinine and potassium is recommended. Clinical trials in heart failure did not include patients with serum creatinine >265 µmol/l (>3 mg/dl).

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

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 risks.

Concomitant therapy with an ACE-inhibitor in heart failure:

The risk of adverse reactions, especially hypotension, hyperkalemia and decreased renal function (including acute renal failure), may increase when CANLOX 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 function impairment:

Exposure to amlodipine is increased in patients with hepatic impairment. Care should be taken when CANLOX is administered in patients with mild to moderate hepatic impairment. Amlodipine should be initiated at the lowest dose and the dose should be increased carefully. Use of CANLOX in patients with severe hepatic impairment is contraindicated.

Hemodialysis:
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, CANLOX should be carefully titrated with thorough monitoring of blood pressure in patients on hemodialysis.

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).

Kidney transplantation
There is limited clinical evidence regarding candesartan cilexetil use in patients who have undergone renal transplant.

Hypotension:
Hypotension may occur during treatment with CANLOX in heart failure patients. As with other drugs that act on the renin-angiotensin-aldosterone system, hypotension may also occur in hypertensive patients with intravascular volume depletion such as those receiving high dose diuretics. Caution should be observed when initiating therapy and correction of hypovolemia should be attempted.

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, CANLOX should be used very carefully in patients suffering from hemodynamic 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 is not recommended in this 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, syncope, hyperkalemia and decreased renal function (including acute renal failure). Concomitant use with ACE inhibitors, angiotensin II receptor blockers or aliskiren is not recommended as it leads to dual blockade of the RAAS (see sections 4.5 and 5.1).

If dual blockade therapy is deemed absolutely necessary, it should only be administered under

specialist supervision, and kidney function, electrolytes and blood pressure should be closely monitored frequently. ACE inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

Hyperkalemia:
Based on experience with other drugs that affect the renin-angiotensin-aldosterone system, concomitant use of candesartan with potassium-sparing diuretics, potassium supplements, artificial salts containing potassium or other medicinal products that may increase potassium levels (e.g. heparin) may lead to increases in serum potassium in hypertensive patients.

Monitoring of potassium should be undertaken as appropriate.

In heart failure patients, hyperkalemia may occur.

Regular monitoring of serum potassium levels is recommended in patients with heart failure, particularly when co-administered with ACE inhibitors and potassium-sparing diuretics (e.g. spironolactone) such as spironolactone. The combination of an ACE inhibitor, a potassium-sparing diuretic (e.g. spironolactone) and CANLOX is not recommended and should be considered only after careful evaluation of the potential benefits and risks.

General:
In patients whose vascular tone and renal function depend predominantly on the activity of the renin-angiotensin-aldosterone system (e.g. patients with severe congestive heart failure or underlying renal disease, including renal artery stenosis), treatment with other medicinal products that affect this system has been associated with acute hypotension, azotaemia, oliguria or, rarely, acute renal failure. The possibility of similar effects cannot be excluded with AIIRAs. 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.

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

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

Pregnancy:
CANLOX 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] (see section 4.8). These patients have complained of abdominal pain, nausea, vomiting, and diarrhea. Symptoms resolved after discontinuation of the angiotensin II receptor blocker. If intestinal angioedema is diagnosed, CANLOX therapy should be discontinued and appropriate monitoring initiated until complete resolution of symptoms occurs.

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

4.5 Interactions with other medicinal products and other forms of interaction
CANLOX can reduce the absorption of tetracyclines due to its magnesium content. Concomitant use is therefore not recommended.

Candesartan:
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.

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

Clinical trial data has shown that dual blockade of the renin-angiotensin-aldosterone system (RAAS) through the combined use of ACE-inhibitors, AIIRA 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).

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.

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

As with ACE inhibitors, concomitant use of 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 levels (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.

Concomitant use with alcohol or anesthetics may aggravate postural 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 pharmaokinetic 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, warfarin or cyclosporine.

Simvastatin

Co-administration of repeated doses of 10 mg of amlodipine with 80 mg simvastatin resulted in a 77% increase in exposure to simvastatin compared to simvastatin alone. The dose of simvastatin should be limited to 20 mg daily in patients receiving amlodipine therapy.

Additional information on special populations:
Hepatic/Renal impairment:
No interaction studies were conducted.

Pediatric population:
Interaction studies were performed only in adults.

4.6 Fertility, pregnancy and lactation
General principles
Pregnancy category: D

Women of child-bearing potential/Birth control (Contraception)
Women of child-bearing potential who use CANLOX have to use effective contraception during treatment.

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

CANLOX is contraindicated in pregnancy.

Patients using CANLOX should be reminded of the possibility of pregnancy before they can determine the appropriate option with their attending physician. When pregnancy is detected, treatment with CANLOX 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 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).

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).

Breast-feeding
It is unknown whether candesartan is excreted in human milk. Candesartan has been observed in the milk of lactating mice. Breastfeeding should be discontinued when the use of CANLOX is necessary, due to the potential 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 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
Candesartan:
In controlled clinical studies adverse reactions were mild and transient and comparable to placebo. The frequency of side effects is not related to dose or age. Withdrawals from treatment due to adverse events were similar with candesartan cilexetil (3.1%) and placebo (3.2%).

In an analysis of cumulative data from clinical trials, the most common adverse events observed with candesartan are shown below. These adverse events are listed based on their frequency of at least 1% greater than placebo. Accordingly, the most commonly reported adverse reactions are dizziness/vertigo, headache, and respiratory tract infection.

The frequency of adverse events listed below by system organ class are defined as follows:
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); unknown (cannot be estimated from the available data).

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
Unknown: Diarrhea

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 disorders
Very rare: Back pain, arthralgia, myalgia

Renal and urinary tract disorders
Very rare: Renal impairment, including renal failure in susceptible patients (see section 4.4)

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

In patients with heart failure:
The adverse effect profile of candesartan cilexetil in heart failure patients was consistent with the pharmacology of the drug and the health status of the patients. In the CHARM clinical program, comparing candesartan cilexetil in doses of 32 mg (n=3,803) to placebo (n=3,796), 21.0% of the candesartan cilexetil group and 16.1% of the placebo group discontinued treatment because of adverse events. The most commonly reported adverse reactions were hyperkalemia, hypotension and renal impairment. These events were more common in patients over 70 years of age, diabetics, or subjects who received other medicinal products which affect the renin-angiotensin- aldosterone system (in particular an ACE inhibitor and/or spironolactone).

The following side effects are reported from clinical studies and post-marketing experience:

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

Metabolism and nutrition disorders
Common: Hyperkalemia
Very rare: Hyponatremia

Nervous system disorders
Very rare: Dizziness, headache

Vascular disorders
Common: Hypotension

Respiratory, thoracic and mediastinal disorders
Very rare: Cough

Gastrointestinal disorders
Very rare: Nausea, intestinal angioedema
Unknown: Diarrhea

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 disorders
Very rare: Back pain, arthralgia, myalgia

Renal and urinary tract disorders
Very rare: Renal impairment, including renal failure in susceptible patients (see section 4.4)

Laboratory findings:
Hyperkalaemia and renal failure are common during treatment of heart failure with candesartan cilexetil. Regular monitoring of serum creatinine and potassium levels is recommended (see section 4.4).

Amlodipine:
Summary of the safety profile
The most commonly observed adverse reactions during treatment are somnolence, dizziness, headache, palpitations, flushing in face, abdominal pain, nausea, ankle swelling, edema and fatigue.

Tabular list of side effects:
The following side effects were 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); unknown (cannot be estimated from the available data).

Blood and the lymphatic system disorders
Very rare: Thrombocytopenia, leucopoenia

Immune system disorders
Very rare: Allergic reaction

Metabolism and nutrition disorders
Very rare: Hyperglycemia

Psychiatric disorders
Uncommon: 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, atrial fibrillation)
Very rare: Myocardial infarction

Vascular disorders
Common: Flushing in face
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 and 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 suspected adverse reactions:

Reporting suspected adverse reactions after authorization 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.

4.9 Overdose

Candesartan:

Symptoms:

Considering the pharmacological properties, the main signs of overdose may be symptomatic hypotension, dizziness and reflex tachycardia. In individual case reports of overdose (of up to 672 mg candesartan cilexetil), patient recovery was uneventful.

Management:

When symptomatic hypotension occurs, symptomatic treatment should be instituted and vital signs of patient monitored. If this is insufficient, plasma volume should be increased by infusion of a solution such as physiological saline. If these measures are insufficient, sympathomimetic drugs may be administered. Candesartan cannot be removed by hemodialysis.

Amlodipine:

In humans experience with intentional overdose is limited.

Symptoms:

Available data suggest that gross overdosage could result in excessive peripheral vasodilatation and possibly reflex tachycardia. A few cases have been reported, starting with marked and possibly prolonged systemic hypotension and progressing to shock with fatal outcome.

Treatment:

Clinically significant hypotension due to amlodipine overdose requires frequent monitoring of cardiac and respiratory function, elevation of the extremities, and active cardiovascular support, including control of 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 antagonists and calcium channel blockers
ATC code: C09DB07

Candesartan

Angiotensin II is the most important vasoactive hormone of the renin-angiotensin-aldosterone system and plays an important role in the physiotherapy of hypertension, heart failure and other cardiovascular disorders. It also plays an important role in the pathogenesis of end-organ damage and hypertrophy. The fundamental physiological effects of angiotensin II, such as vasoconstriction,

stimulation of aldosterone release, regulation of salt and water balance, and stimulation of cell growth, are mediated through the AT_1 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 that selectively binds tightly to AT_1 receptors and dissociates slowly. It has no agonist activity.

Candesartan does not inhibit ACE, which converts angiotensin I to angiotensin II and degrades bradykinin. Bradykinin has no effect on substance P or ACE. 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 AT_1 receptors results in dose related increases in plasma renin levels, angiotensin I and angiotensin II levels, and a decrease in plasma aldosterone concentration.

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 evidence of severe hypotension after the first dose or of a rebound effect after discontinuation of therapy.

After administration of a single dose of candesartan cilexetil, onset of antihypertensive effect generally occurs within 2 hours. When the drug is used continuously at any dose, most of the reduction in blood pressure is usually achieved within 4 weeks, and this level of blood pressure is maintained with long-term therapy. 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 randomized, double-blind studies in a total of 1,268 patients with mild to moderate hypertension. The 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, $p<0.0001/p<0.0001$).

Candesartan cilexetil has an additive antihypertensive effect when used with hydrochlorothiazide. Candesartan was well tolerated when used 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 19.0/12.7 mmHg, $p<0.0001/p<0.0001$).

Candesartan increases renal blood flow while decreasing renal vascular resistance and filtration fraction, increasing glomerular filtration rate or having no effect. In a 3-month clinical study in hypertensive patients with type II *diabetes mellitus* and microalbuminuria, 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 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). Another antihypertensive treatment was added to the candesartan cilexetil or placebo groups 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 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.

The ONTARGET study was conducted in patients with a history of cardiovascular or cerebrovascular disease or type 2 diabetes mellitus associated with end-organ damage. NEPHRON-D was conducted in patients with Type 2 diabetes mellitus and diabetic nephropathy.

These studies did not show significant benefit on renal and/or cardiovascular outcomes and mortality, and an increased risk of hyperkalemia, acute kidney injury and/or hypotension was observed compared with monotherapy. Given their similar pharmacodynamic properties, these results are also relevant for other ACE-inhibitors and AIIRA.

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.

Heart Failure
Treatment with candesartan cilexetil reduces mortality, hospitalization due to heart failure, and improves symptoms in patients with left ventricular systolic dysfunction as shown in the Candesartan in Heart failure – Assessment of Reduction in Mortality and morbidity (CHARM) program.

CHARM-Alternative (n=2,028) included patients with LVEF ≤40% who could not take an ACE inhibitor because they could not tolerate it (mainly due to cough, 72%); CHARM-Added (n=2,548) included patients with LVEF ≤40% who were treated with an ACE inhibitor; and CHARM-Preserved (n=3,023) included patients with LVEF >40%.

Patients initially receiving optimal chronic heart failure therapy were randomized to receive either placebo or candesartan cilexetil (4 mg or 8 mg once daily, titrated to 32 mg once daily or the highest tolerated dose, with a mean dose of 24 mg) and were followed for a mean of 37.7 months. After 6 months of treatment 63% of the patients still taking candesartan cilexetil (89%) were at the target dose of 32 mg.

In the CHARM-Alternative study, the composite endpoint of cardiovascular mortality or first hospitalization due to chronic heart failure was significantly reduced with candesartan compared to placebo (relative risk (hazard ratio)-HR- 0.77, 95% confidence interval 0.67-0.89, p<0.001). This corresponds to a relative risk reduction of 23%. To prevent a patient's death due to a cardiovascular event or hospitalization for heart failure treatment, 14 patients needed to be treated throughout the study.

The composite endpoint of all-cause mortality or first chronic heart failure hospitalization was also significantly reduced with candesartan (relative risk (hazar ratio) 0.80 (95% CI: 0.70 to 0.92, p=0.001). The mortality and morbidity (hospitalization due to chronic heart failure) components of the composite endpoint contributed to the positive effect of candesartan. Treatment with candesartan cilexetil resulted in improvement in NYHA functional class (p=0.008).

In CHARM-Added study, the composite endpoint of cardiovascular mortality or first chronic heart failure hospitalization was significantly reduced with candesartan in comparison with placebo, relative risk (HR) 0.85 (95% CI: 0.75 to 0.96, p=0.011). This corresponds to a relative risk reduction of 15%. To prevent one patient from dying from a cardiovascular event or being hospitalized for heart failure treatment, 23 patients needed to be treated throughout the study.

The composite endpoint of all-cause mortality or first chronic heart failure hospitalization was also significantly reduced with candesartan, (relative risk (hazard ratio) 0.87 (95% CI: 0.78 to 0.98, p=0.021). The mortality and morbidity components of the composite endpoint contributed to the beneficial effect of candesartan. Treatment with candesartan cilexetil resulted in improved NYHA functional class (p=0.020).

In CHARM-Preserved study, no statistically significant reduction was achieved in the composite endpoint of cardiovascular mortality or first chronic heart failure hospitalization, (relative risk (hazard ratio) 0.89 (95% CI: 0.77 to 1.03, p=0.118).

All-cause mortality was not statistically significant when examined separately in each of the three CHARM studies. However, all-cause mortality was also assessed in pooled populations, CHARM-Alternative and CHARM-Added, (hazard ratio) 0.88 (95% CI: 0.79 to 0.98, p=0.018) and all three studies, (hazard ratio, 0.91, 95% CI: 0.83 to 1.00, p=0.055).

The beneficial effects of candesartan on cardiovascular mortality and hospitalization for chronic heart failure are the same in all patients, regardless of age, gender, or combination therapy. Candesartan is also effective in patients receiving concomitant beta-blockers and ACE inhibitors, whether the patient is receiving the ACE inhibitor at the recommended dose or at a different dose.

In patients with chronic heart failure and impaired left ventricular systolic function (left ventricular ejection fraction, LVEF ≤40%), candesartan decreases systemic vascular resistance and pulmonary capillary wedge pressure, increases plasma renin activity and angiotensin II concentration, and decreases aldosterone levels.

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.

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, double-blind, placebo-controlled study of 1997 patients; Comparison of Amlodipine vs. Enalapril to Limit Occurrences of Thrombosis (CAMELOT)[2]. Of these patients, 655 were treated with placebo and 663 with amlodipine 5 to 10 mg for 2 years, in addition to standard care of statins, beta-blockers, diuretics, and aspirin. Main efficacy results are shown in Table 1. The results showed that amlodipine treatment reduced angina-related hospitalizations and revascularization attempts 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)	.003
Individual Components					
Coronary revascularization	78 (11.8)	103 (15.7)	95 (14.1)	0.73 (0.54- 0.98)	.03
Hospitalization for angina	51 (7.7)	84 (12.8)	86 (12.8)	0.58 (0.41- 0.82)	.002
Nonfatal myocardial infarction	14 (2.1)	19 (2.9)	11 (1.6)	0.73 (0.37- 1.46)	.37
Stroke or transient ischemic attack	6 (0.9)	12 (1.8)	8 (1.2)	0.50 (0.19- 1.32)	.15
Cardiovascular death	5 (0.8)	2 (0.3)	5 (0.7)	2.46 (0.48- 12.7)	.27
Hospitalization for congestive heart failure	3 (0.5)	5 (0.8)	4 (0.6)	0.59 (0.14- 2.47)	.46
Resuscitated cardiac arrest	0	4 (0.6)	1 (0.1)	NA	.04
New-onset peripheral vascular	5 (0.8)	2 (0.3)	8 (1.2)	2.6 (0.5- 13.4)	.24

disease					

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 measures and clinical symptomatology.

A placebo-controlled study (PRAISE) in patients with NYHA Class III to IV heart failure receiving digoxin, diuretics, and angiotensin-converting enzyme (ACE) inhibitors showed that amlodipine did not increase the risk of mortality or combined mortality and morbidity in patients with heart failure.

In a long-term, placebo-controlled follow-up study (PRAISE-2) in patients with NYHA Class III and IV heart failure of non-ischaemic aetiology receiving stable doses of ACE inhibitors, digitalis and diuretics, amlodipine had no effect on total or cardiovascular mortality. In this same population amlodipine was associated with increased reports of pulmonary edema, despite no significant difference in the incidence of worsening heart failure as 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 (calcium channel blocker) (2.5-10 mg/d) and lisinopril (angiotensin-converting-enzyme inhibitor (ACE) inhibitor) (10-40 mg/d) as initial 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 cardiovascular (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%), 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 [0.90-1.07] 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.

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
Candesartan

General properties
Absorption:
Following oral administration, candesartan cilexetil is converted to the active substance candesartan. The absolute bioavailability of candesartan is approximately 40% after taking an oral

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

The bioavailability of candesartan is not affected by food.

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

Biotransformation:
Available interaction studies indicate that candesartan has no effect on CYP2C9 and CYP3A4. Based on *in vitro* data, no *in vivo* interaction would be expected to occur between candesartan and medicinal product whose metabolism is dependent upon cytochrome P450 isoenzymes CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1 or CYP3A4.

Elimination:
The terminal half-life (t½) of candesartan is approximately 9 hours. There is no accumulation following multiple doses.

Candesartan is mainly excreted unchanged through the urine and bile, with a very small proportion excreted after being metabolized in the liver (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-labeled 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.

Characteristic features in patients:
Pharmacokinetic 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 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 of patients undergoing hemodialysis 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

General properties

Absorption:

After oral administration of therapeutic doses, amlodipine is well absorbed and forms peak blood levels between 6-12 hours post dose. Absolute bioavailability has been calculated to be between 64 and 80%.

The bioavailability of amlodipine is not affected by food intake.

Distribution:

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:

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:

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

Linearity/Non-linearity:

Data is not available.

Characteristic features in patients:

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 area under the cure (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.

Use in 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%.

Use in 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. 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 (CUF) 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

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 have shown late fetal and neonatal damage to the kidney. The mechanism is thought to be via pharmacological action on the renin-angiotensin-aldosterone system. Renal effects (such as interstitial nephritis, tubular distension, basophilic tubulitis, increased plasma urea and creatinine levels) may occur secondary to the hypotensive effect of candesartan leading to impaired 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.

In preclinical studies in normotensive neonatal and juvenile rats, candesartan caused a reduction in body weight and heart weight. As in adult animals, these effects are considered to result from the pharmacological action of candesartan. At the lowest dose of 10 mg/kg exposure to candesartan was between 12 and 78 times the levels found in children aged 1 to <6 who received candesartan cilexetil at a dose of 0.2 mg/kg and 7 to 54 times those found in children aged 6 to <17 who received candesartan cilexetil at a dose of 16 mg. As a no observed effect level was not identified in these studies, the safety margin for the effects on heart weight and the clinical relevance of the finding is unknown.

Fetotoxicity 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.

The renin-angiotensin-aldosterone system plays a critical role in kidney development in utero.

Renin-angiotensin-aldosterone system blockade has been shown to lead to abnormal kidney development in very young mice. Administering drugs that act directly on the renin-angiotensin-aldosterone system can alter normal renal development. Therefore, children aged less than 1 year should not receive candesartan cilexetil (see section 4.3).

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:
Mouse and rats 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 (on a mg/m^2 basis, it is similar to the maximum recommended human clinical dose

of 10 mg for mice and twice the maximum recommended human clinical dose of 10 mg for rats*) 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:
In rats, no effects on fertility were observed at doses up to 10 mg/kg/day (eight times the maximum recommended human dose of 10 mg on a mg/m^2 basis*) (64 days in males and 14 days in females prior to mating). 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.

* Patient weight is assumed to be 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

There are no known incompatibilities.

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

It is packaged in blisters made of PA/ALU/PVC foil/aluminum foil as the primary packaging material. The blisters are packaged in cardboard boxes. Each box contains 28 tablets and is presented in blister packs along with package leaflet.

6.6 Special precautions for disposal and other handling

Any unused material should be disposed according to local disposal regulations.

7. MARKETING AUTHORIZATION HOLDER

DEVA Holding A.Ş.
Halkalı Merkez Mah. Basın Ekspres Cad. No:1

34303 Küçükçekmece – Istanbul/TÜRKİYE
Phone: +90 212 692 92 92
Fax: +90 212 697 00 24
E-mail: deva@devaholding.com.tr

8. MARKETING AUTHORIZATION NUMBER
2019/319

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION
Date of first authorization: 27.06.2019
Date of last renewal:

10. DATE OF REVISION OF THE TEXT