SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
CANDEXIL PLUS 16 mg/12.5 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Active substance(s):
Candesartan cilexetil_____16 mg
Hydrochlorothiazide_____12.5 mg
Excipient(s) with known effect:
Lactose monohydrate 200 M (from cow's milk)_____62.08 mg
Lactose monohydrate DCL 15 (from bovine milk)_____5.71 mg
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Tablet.
Light yellow, slightly biconvex, oblong tablets with a score in the middle on one side (the score is solely intended to break the tablet for a facile swallowing, not to divide it into equal doses).

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
Essential hypertension when monotherapy with candesartan cilexetil or hydrochlorothiazide is not sufficiently effective (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 of CANDEXIL PLUS is one tablet once daily. Dose titration with candesartan cilexetil and hydrochlorothiazide is recommended.

When clinically appropriate, a direct change from monotherapy to CANDEXIL PLUS may be considered. Dose titration of candesartan cilexetil is recommended when switching from hydrochlorothiazide monotherapy. CANDEXIL PLUS may be administered in patients whose blood pressure is not optimally controlled with candesartan cilexetil or hydrochlorothiazide monotherapy or CANDEXIL PLUS at lower doses (see sections 4.3, 4.4, 4.5, and 5.1).

Most of the antihypertensive effect is usually attained within 4 weeks of initiation of treatment.

Method of administration
For oral administration.
The bioavailability of candesartan is not affected by food.
There is no clinically significant interaction between hydrochlorothiazide and food.

Additional information on special populations
Renal impairment
Loop diuretics are preferred to thiazides in patients with 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 CANDEXIL PLUS (the recommended starting dose of candesartan cilexetil is 4 mg in these patients). CANDEXIL PLUS is contraindicated in patients with severe renal impairment (creatinine clearance <30 ml/min/1.73 m² BSA (see section 4.3).

Hepatic impairment
Dose titration of candesartan cilexetil is recommended in patients with mild to moderate hepatic impairment before treatment with CANDEXIL PLUS (the recommended starting dose of candesartan cilexetil is 4 mg in these patients).

CANDEXIL PLUS is contraindicated in patients with severe hepatic impairment and/or cholestasis (see section 4.3).

Pediatric population
The safety and efficacy of candesartan cilexetil/hydrochlorothiazide combination in children aged between birth and 18 years have not been established. No data are available.

Geriatric population
No dose adjustment is necessary in elderly patients.

Patients with intravascular volume depletion
Dose titration of candesartan cilexetil is recommended in patients at risk for hypotension, such as patients with possible intravascular volume depletion (an initial dose of candesartan cilexetil of 4 mg may be considered in these patients).

4.3 Contraindications
- Hypersensitivity to any component of CANDEXIL PLUS or to sulfonamide-derived medicines (hydrochlorothiazide is a sulfonamide derivative)
- 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
- Refractory hypokalemia and hypocalcemia
- Gout disease
- Concomitant use of CANDEXIL PLUS with aliskiren-containing products 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/Kidney transplantation
Loop diuretics are preferred to thiazides in this population. When the combination of candesartan cilexetil/hydrochlorothiazide is used in patients with renal impairment, a periodic monitoring of potassium, creatinine and uric acid levels is recommended.

There is no adequate clinical data regarding the administration of the combination of candesartan cilexetil/hydrochlorothiazide in patients with recent kidney transplantation.

As with other medicinal products that inhibit the renin-angiotensin-aldosterone system, changes in renal function may be expected in susceptible patients treated with the combination of candesartan cilexetil/hydrochlorothiazide (see section 4.3).

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 may be observed also with angiotensin II receptor antagonists.

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 CANDEXIL PLUS is not recommended until this condition has been corrected (The recommended starting 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.

Hepatic impairment
Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma. There is no clinical experience with CANDEXIL PLUS in patients with hepatic impairment.

Non-melanoma skin cancer
In two epidemiological studies based on the Danish National Cancer Registry, an increased risk of non-melanoma skin cancer, in the form of basal cell and squamous cell carcinoma, has been observed with increasing cumulative hydrochlorothiazide exposure. The photosensitizing action of hydrochlorothiazide could be involved as a possible mechanism for non-melanoma skin cancer development.

Patients using hydrochlorothiazide should be informed of the risk of non-melanoma skin cancer and advised to regularly check their skin for new lesions and to promptly report any suspicious skin changes. Preventive measures such as limited sunlight/UV exposure and, in the event of exposure, adequate sun protection should be recommended to patients in order to minimize the risk of skin cancer. Suspicious skin changes should be promptly examined, potentially via histological examinations of biopsies. The use of hydrochlorothiazide may also need to be reconsidered in patients with a previous history of non-melanoma skin cancer (see also section 4.8).

Choroidal effusion, acute myopia, and angle-closure glaucoma
Hydrochlorothiazide, a sulfonamide, can trigger an idiosyncratic reaction that can lead to choroidal effusion with visual field defects, transient myopia and acute angle-closure glaucoma. Symptoms include rapid onset of decreased visual acuity or eye pain and typically appear within hours to weeks after the start of therapy. Untreated angle closure glaucoma can lead to permanent loss of vision. Primary therapy consists of immediate discontinuation of the medicinal product. If intraocular pressure remains elevated, immediate medical treatment or surgery must be considered. Risk factors for developing angle-closure glaucoma may be a history of sulfonamide or penicillin allergy.

Aortic and mitral valve stenosis or obstructive hypertrophic cardiomyopathy
As with other vasodilators, special caution is indicated for use of CANDEXIL PLUS 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 CANDEXIL PLUS is not recommended in this population.

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, hypomagnesaemia and hypochloremic alkalosis).

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).

CANDEXIL PLUS should not be used in patients with low level potassium in the blood.

Treatment with candesartan cilexetil may cause hyperkalemia, especially in the presence of heart failure and/or renal impairment. Concomitant use of CANDEXIL PLUS and other medicines that affect the renin-angiotensin-aldosterone system, concomitantly administered ACE inhibitors, aliskiren, potassium-sparing diuretics, potassium preparations, salt substitutes containing potassium or other medicines that may increase serum potassium levels (e.g. heparin sodium, combination of trimethoprim/sulfamethoxazole) 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.

Metabolite and endocrine effects
Treatment with a thiazide diuretic may impair glucose tolerance. Dose adjustments of antidiabetic medicinal products, including insulin, may be required. Latent diabetes mellitus may manifest during thiazide therapy. Increase in cholesterol and triglyceride levels is associated with thiazide diuretic treatment. However, these effects are very little with 12.5 mg of thiazide dose in CANDEXIL PLUS. Thiazide diuretics cause increase in serum uric acid concentration and may cause 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.

Intestinal angioedema:
Intestinal angioedema has been reported in patients treated with angiotensin II receptor blockers [including candesartan] (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, CANDEXIL® PLUS treatment should be discontinued and appropriate monitoring should be initiated until symptoms fully resolve.

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 (also including AIIRAs (angio-tensin type II receptor antagonists)) has been associated with acute hypotension, azotemia, oliguria or, rarely, acute renal failure. 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 of allergy or bronchial asthma.

With thiazide diuretics, systemic *lupus eritamatozus* may get activated or exacerbated.

The antihypertensive effect of CANDEXIL PLUS may be enhanced by other antihypertensive products.

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

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 section 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.

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 CANDEXIL 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.

Acute Respiratory Toxicity
Very rare cases of severe acute respiratory toxicity, including acute respiratory distress syndrome (ARDS), have been reported following ingestion of hydrochlorothiazide. Pulmonary edema typically develops within minutes to hours after ingestion of hydrochlorothiazide. Initial symptoms include dyspnea, fever, pulmonary deterioration, and hypotension. If a diagnosis of ARDS is suspected, CANDEXIL PLUS treatment should be discontinued and appropriate therapy instituted.

Hydrochlorothiazide should not be administered to patients who have previously experienced ARDS following hydrochlorothiazide ingestion.

CANDEXIL PLUS Tablet contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interactions with other medicinal products and other forms of interaction

Compounds which have been investigated in clinical pharmacokinetic studies include warfarin, digoxin, oral contraceptives (i.e. ethinylestradiol/levonorgestrel), glibenclamide and nifedipine. No pharmacokinetic interactions of clinical significance were identified in these studies.

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

Diuretic-induced hypokalemia and hypomagnesaemia predisposes to the potential cardiotoxic effects of digitalis glycosides and antiarrhythmics. Periodic monitoring of serum potassium is recommended when CANDEXIL PLUS is administered with such medicinal products.

- 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, cymemazine, sulpiride, sultopride, amisulpride, tiapride, pimozide, haloperidol, droperiodol)
- Other (e.g. bepridil, cisapride, diphemanil, erythromycin IV, halofantrine, ketanserine, mizolastine, pentamidine, sparfloxacin, 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 has also been reported with AIIRAs. Use of candesartan and hydrochlorothiazide with lithium is not recommended. If the combination proves necessary, careful monitoring of serum lithium levels is recommended.

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

As with ACE inhibitors, concomitant use of AIIRAs and NSAIDs may lead to an increased risk of worsening of renal function, including possible acute renal failure, and an increase in serum potassium, (especially in patients with poor pre-existing renal function). The combination should be administered with caution, especially in the elderly.

Patients should be adequately hydrated and consideration should be given to monitoring renal function after initiation of concomitant therapy, and periodically thereafter.

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 nondepolarizing skeletal muscle relaxants (eg, 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.

Avoid using CANDEXIL PLUS in patients with hypercalcemia.

The hyperglycemic effects of beta-blockers and diazoxide may be enhanced with 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.

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

If you are consuming alcohol, talk with your doctor before taking CANDEXIL PLUS. Fainting and dizziness has been observed in some patients using alcohol while on CANDEXIL PLUS therapy.

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 substances.

Concomitant treatment with cyclosporine may increase 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.

Concomitant use with aliskiren
Clinical trial data has shown that dual blockade of the renin-angiotensin-aldosterone system (RAAS) through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is associated with a higher frequency of adverse events such as hypotension, 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)

Additional information on special populations
No particular interaction study has been conducted on this population.

Pediatric population
No particular interaction study has been conducted on this population.

4.6 Fertility, pregnancy and lactation
General principles

Pregnancy category "D".

Women of child-bearing potential/Contraception
Patients who plan to get pregnant or suspect that they may be pregnant should stop using CANDEXIL PLUS immediately.

Pregnancy
CANDEXIL PLUS has harmful pharmacological effects on pregnancy and/or fetus/neonate. CANDEXIL PLUS is contraindicated during pregnancy (see section 4.3). Patients who use CANDEXIL PLUS should be reminded of the possibility of getting pregnant beforehand for them to be able to determine the appropriate alternative with their physicians who treat them. When pregnancy is diagnosed, treatment with CANDEXIL PLUS should be stopped immediately and, if appropriate, alternative therapy should be started.

Medicinal products with direct effect on renin-angiotensin system may lead to fetal and neonatal damage and even death. It is known that angiotensin II receptor antagonist treatment causes 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, it use during pregnancy may compromise feto-placental perfusion and may cause fetal or neonatal effects such as hepatitis, electrolyte imbalance and thrombocytopenia.

Hydrochlorothiazide should not be used for gestational edema, gestational hypertension or preeclampsia due to the risk of decreased plasma volume and placental hypoperfusion, without a beneficial effect on the course of the disease.

Hydrochlorothiazide should not be used for essential hypertension in pregnant women except in rare situations where no other treatment could be used.

Breast-feeding
Angiotensin II Receptor Antagonists (AIIRAs):
Because no information is available regarding the use of CANDEXIL PLUS during breastfeeding, CANDEXIL PLUS is not recommended and alternative treatments with better established safety profiles during breast feeding are preferable, especially while nursing a newborn or preterm infant.

Hydrochlorothiazide:
Hydrochlorothiazide is excreted in human milk in small amounts. Thiazides in high doses causing intense diuresis can inhibit the milk production. The use of CANDEXIL PLUS during breast-feeding is not recommended.

Fertility
No data are available.

4.7 Effects on ability to drive and use machines
No studies on the effects on the ability to drive and use machines have been performed. When driving vehicles or operating machines, it should be taken into account that occasionally dizziness or weariness may occur during treatment with CANDEXIL PLUS. Therefore caution should be taken while driving and using machines.

4.8 Undesirable effects
In controlled clinical studies with candesartan cilexetil/hydrochlorothiazide adverse events were mild and transient. Withdrawals from treatment due to adverse events were similar with candesartan cilexetil/hydrochlorothiazide (2.3 - 3.3%) and placebo (2.7 – 4.3%).

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 from clinical trials and post-marketing experience in relation to candesartan cilexetil are presented below. In a pooled analysis of clinical trial data of hypertensive patients, adverse reactions with candesartan cilexetil were defined based on an incidence of adverse events with candesartan cilexetil at least 1% higher than the incidence seen with placebo.

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); not known (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, acute respiratory distress syndrome (ARDS) (see section 4.4)

Gastrointestinal disorders
Very rare: Nausea, intestinal angioedema
Not known: 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 and bone disorders

Very rare: Back pain, arthralgia, myalgia

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

Adverse reactions with hydrochlorothiazide monotherapy usually with doses of 25 mg or higher are presented below.

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

Blood and lymphatic system disorders
Rare: Leucopenia, 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 hyperkalemia)

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, choroidal effusion

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 pneumonia and pulmonary edema)

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
Not known: Systemic *lupus erythematosus*, cutaneous *lupus erythematosus*

Musculoskeletal system disorders, connective tissue and bone disorders
Rare: Muscle spasm

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

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

Investigations
Common: Increases 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 also sections 4.4 and 5.1).

Reporting of side effects
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
Symptoms
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.

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

When indicated, induction of vomiting or gastric lavage should be considered.

If symptomatic hypotension should occur, symptomatic treatment should be instituted and vital signs of the patient 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group : Angiotensin II Antagonists and Diuretics
ATC code : C09DA06

Mechanism of action

Angiotensin II is the primary vasoactive hormone of the Renin-Angiotensin-Aldosterone System and plays a prominent role in the pathophysiology of hypertension and other cardiovascular disorders. It also has a prominent 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 (AT_1) receptor.

Pharmacodynamic properties

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 AT_1 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, it is 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 (AT_1) receptors results in dose related increases in plasma renin levels, angiotensin I and angiotensin II levels, and a decrease in plasma aldosterone concentration.

Clinical efficacy and safety

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 4937 elderly patients (aged 70-89 years; 21% aged 80 or above) with mild to moderate hypertension (SBP 160-179 mmHg and/or DBP 90-99 mmHg) 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 30.0 events per 1000 patient-years in the control group (relative risk 0.89, 95% CI 0.75 to 1.06, p=0.19).

Non-melanoma skin cancer: Based on available data from epidemiological studies, cumulative dose-dependent association between HCTZ and NMSC has been observed. One study included a population comprised of 71,533 cases of BCC and of 8,629 cases of SCC matched to 1,430,833 and 172,462 population controls, respectively. High HCTZ use (≥50,000 mg cumulative) was associated with an adjusted OR of 1.29 (95% CI: 1.23-1.35) for BCC and 3.98 (95% CI: 3.68-4.31) for SCC. A clear cumulative dose response relationship was observed for both BCC and SCC. Another study showed a possible association between lip cancer (SCC) and exposure to HCTZ: 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).

Hydrochlorothiazide inhibits re-absorption of sodium in distal renal tubules and causes higher 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.

Candesartan and hydrochlorothiazide have additive antihypertensive effects.

In hypertensive patients, combination of candesartan and hydrochlorothiazide enables an effective and long-lasting reduction in arterial blood pressure without reflex increase in heart rate. There is no indication of first dose severe hypotension or rebound effect after cessation of treatment. After administration of a single dose of, 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 4 weeks and is sustained during long-term treatment. Combination of candesartan and 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 randomized, double-blind study, combination of candesartan and hydrochlorothiazide once daily enables significantly more effective and regular control of blood pressure of higher number of patients over 24 hours, compared to other combinations containing angiotensin II receptor antagonist 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.

In two clinical studies (randomized, double-blind, placebo controlled, parallel group) including 275 and 1524 randomized patients**,** respectively, 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 monocomponents.

In a randomized, double-blind, parallel group clinical study including 1975 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.

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 angiotensin II receptor blocker in patients with type 2 diabetes mellitus and chronic kidney disease, cardiovascular disease, or both. The study was terminated early because of an increased risk of adverse outcomes. Cardiovascular death and stroke were both numerically more frequent in the aliskiren group than in the placebo group and adverse events and serious adverse events of interest (hyperkalemia, hypotension and renal dysfunction) were more frequently reported in the aliskiren group than in the placebo group.

5.2 Pharmacokinetic properties

General properties

Concomitant administration of candesartan cilexetil/hydrochlorothiazide has no clinically significant effect on the pharmacokinetics of either medicinal product constituting the combination.

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 the tablet formulation compared with the same oral solution is approximately 34%. 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.

Hydrochlorothiazide

Following oral administration, hydrochlorothiazide is rapidly absorbed from the gastrointestinal tract with absolute bioavailability of 70%. Concomitant intake of food increases the absorption by 15%. The bioavailability may be decreased in patients with cardiac failure and marked edema.

Distribution

Candesartan cilexetil

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

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

Biotransformation
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. There is no accumulation following multiple doses. Half-life of candesartan (approximately 9 hours) does not change when candesartan cilexetil is co-administered with hydrochlorothiazide. Following repeated doses of combined preparation, candesartan does not accumulate more compared to mono-therapy.

Hydrochlorothiazide
The terminal half-life ($t_{1/2}$) of hydrochlorothiazide is approximately 8 hours. About 70% of the oral dose is eliminated in urine within 48 hours. Half-life of hydrochlorothiazide does not change when it is co-administered with candesartan (approximately 8 hours). Following repeated doses of combined preparation, hydrochlorothiazide does not accumulate more compared to mono-therapy.

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
Hydrochlorothiazide is not metabolized and is excreted almost entirely as unchanged drug by glomerular filtration and active tubular secretion.

Linearity/non-linearity:
No data found.

Other special populations
Candesartan cilexetil:
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 in young and elderly patients (see section 4.2).

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

AUC of candesartan in patients with mild to moderate hepatic impairment was increased by 23% approximately.

Hydrochlorothiazide:
The terminal half-life of hydrochlorothiazide is prolonged in patients with renal dysfunction.

5.3 Preclinical safety data
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 indicate late fetal and neonatal damage to kidney. The mechanism is through to be mediated by pharmacological effect on renin-angiotensin-aldosterone system. Effects on the kidneys (such as interstitial nephritis, tubular distension, basophilic tubules; increased plasma concentrations of urea and creatinine) were induced by candesartan which could be secondary to the hypotensive effect leading to alterations of renal perfusion. Addition of hydrochlorothiazide causes increase in 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. In rats, mice or rats; addition of hydrochlorothiazide does not have significant effect on results of fetal development studies (see section 4.6).

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

There was no evidence of carcinogenicity.

6. PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Lactose monohydrate 200 M (from cow's milk)
Lactose monohydrate DCL 15 (from bovine milk)
Maize starch
Carboxymethyl cellulose calcium
Hydroxypropyl cellulose
Iron oxide yellow (E172)
Polyethylene glycol 8000
Magnesium stearate

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
36 months.

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

6.5 Nature and contents of packaging
Blisters including 14 tablets each, coated with transparent PVDC on one side and printed aluminum foil on the other side. Each cardboard box contains 28 or 84 tablets.

6.6 Special precautions for disposal and other handling
No particular requirement. 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 – İSTANBUL / TÜRKİYE

8. MARKETING AUTHORIZATION NUMBER
214/3

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION
Date of first authorization : 28.12.2007
Date of last renewal :

10. DATE OF REVISION OF THE TEXT