SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

CANDEXIL 16 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance:
Candesartan cilexetil ……16 mg
Excipient(s):
See section 6.1 for excipients.

3. PHARMACEUTICAL FORM

Tablet.
Red-coloured, round, one side scored, biconvex tablets.
CANDEXIL 16 mg tablets can be broken along the central score line to form two equal parts.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Primary hypertension (see Sections 4.3, 4.4, 4.5, and 5.1).

Heart failure and impaired left ventricular systolic function (left ventricular ejection fraction ≤ 40%) or as an adjunct to ACE inhibitors in patients with symptomatic heart failure despite optimal therapy when mineralocorticoid receptor antagonists are not tolerated (see Sections 4.2, 4.4, 4.5 and 5.1).

4.2 Posology and method of administration

Dosage/frequency and duration of administration:
Hypertension:
The recommended initial dose and normal maintenance dose of CANDEXIL is 8 mg once daily. The majority of the antihypertensive effect is achieved within 4 weeks of starting treatment.

In some patients whose blood pressure is not adequately controlled, the dose may be increased to 16 mg once daily and up to a maximum of 32 mg once daily. Treatment should be adjusted according to the desired blood pressure response. CANDEXIL may also be administered with other antihypertensive agents (see Sections 4.3, 4.4, 4.5 and 5.1). The addition of hydrochlorothiazide demonstrates an additional antihypertensive effect with various doses of CANDEXIL.

Additional information on specific populations:
Renal impairment:
The recommended initial dose in patients with renal impairment, including haemodialysis patients, is 4 mg once daily. The dose should be adjusted according to the patient's response.

Clinical experience with candesartan in patients with very severe or end-stage renal impairment (creatinine clearance < 15 mL/minute) is limited (see Section 4.4).

Hepatic impairment:
The recommended starting dose for patients with mild to moderate hepatic impairment is 4 mg once daily. The dose may be adjusted according to the patient's response. CANDEXIL is contraindicated in patients with severe hepatic impairment and/or cholestasis (see Sections 4.3 and 5.2).

Geriatric population:
No adjustment of the initial dose is required in the elderly.

Paediatric population:
The safety and efficacy of candesartan in children and adolescents (under 18 years of age) have not been established.

Use in patients with intravascular fluid loss:
In patients at risk of hypotension, such as those with a potential for intravascular fluid loss, an initial dose of 4 mg is recommended (see Section 4.4).

Use in black patients:
The antihypertensive effect of candesartan is less pronounced in black patients than in non-black patients. Consequently, CANDEXIL titration and combination therapy may be required more frequently in black patients than in non-black patients (see Section 5.1).

Heart failure
The recommended initial dose of CANDEXIL is 4 mg once daily. The target daily dose of 32 mg or the maximum tolerated dose is achieved by doubling the dose at intervals of at least 2 weeks (see Section 4.4). The assessment of patients with heart failure should include evaluation of renal function by monitoring serum creatinine and potassium levels. CANDEXIL may be administered concomitantly with other heart failure treatments containing ACE inhibitors, beta-blockers, diuretics, and digitalis, or a combination of these drugs. CANDEXIL may be administered as an adjunct to ACE inhibitors in patients with symptomatic heart failure despite optimal standard heart failure therapy when mineralocorticoid receptor antagonists are not tolerated. A combination of an ACE inhibitor, a potassium-sparing diuretic and CANDEXIL is not recommended; this combination should only be considered after careful evaluation of the potential benefits and risks (see Sections 4.4, 4.8 and 5.1).

Additional information on specific populations:
No adjustment of the initial dose is required in elderly patients or in patients with intravascular fluid depletion, renal impairment, or mild to moderate hepatic impairment.

Paediatric population:
The efficacy and safety of candesartan in the treatment of hypertension and heart failure in children up to 18 years of age have not been established. No data are available.

Administration:
CANDEXIL should be administered once daily. It may be taken with or without food. The bioavailability of candesartan is not affected by food.

4.3 Contraindications
- In individuals with hypersensitivity to any of the ingredients in CANDEXIL.
- During pregnancy and breastfeeding (see Section 4.6).
- Severe hepatic impairment and/or cholestasis,
- The concomitant use of CANDEXIL with aliskiren-containing medicines is contraindicated in patients with diabetes mellitus or renal impairment (GFR <60 ml/min/1.73 m^2) (see Sections 4.5 and 5.1).

4.4 Special warnings and precautions for use
Dual blockade of the renin-angiotensin-aldosterone system (RAAS):
There is evidence that the combined use of ACE inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, syncope, hyperkalaemia and reduced renal function (including acute renal failure). As this leads to dual blockade of the RAAS, the concomitant use of ACE inhibitors, angiotensin II receptor blockers or aliskiren is not recommended (see Sections 4.5 and 5.1).

If dual blockade therapy is deemed absolutely necessary, it should only be administered under specialist supervision, and renal function, electrolytes and blood pressure should be closely monitored. ACE inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

Renal Impairment:
As with other drugs that inhibit the renin-angiotensin-aldosterone system, changes in renal function may be expected in sensitive patients treated with CANDEXIL.

When CANDEXIL is used in hypertensive patients with renal impairment, serum potassium and creatinine levels should be measured regularly. Experience with its use in patients with very severe or end-stage renal impairment (creatinine clearance <15 mL/min) is limited. In these patients, the CANDEXIL dose should be carefully titrated with close monitoring of blood pressure.

Particularly in patients over 75 years of age and with renal impairment, renal function should be monitored regularly to assess for heart failure. Monitoring serum creatinine and potassium

levels is recommended when titrating the CANDEXIL dose. Clinical studies in heart failure did not include patients with serum creatinine levels >265 micromoles/L (>3 mg/dL).

Use with ACE inhibitors in heart failure:
When CANDEXIL is used in combination with an ACE inhibitor, the risk of adverse reactions, particularly hypotension, hyperkalaemia, and decreased renal function (including acute renal failure), may be increased. A triple combination of an ACE inhibitor, a mineralocorticoid receptor antagonist and candesartan is not recommended. These combinations should be used under specialist supervision and renal function, electrolytes and blood pressure should be closely monitored.

ACE inhibitors and angiotensin II receptor blockers should not be used together in patients with diabetic nephropathy.

Haemodialysis:
During dialysis, blood pressure may be particularly sensitive to AT_1-receptor blockade due to decrease in plasma volume and activation of the renin-angiotensin-aldosterone system. Therefore, in haemodialysis patients, blood pressure should be closely monitored and the CANDEXIL dose carefully titrated.

Renal artery stenosis:
Angiotensin receptor blockers, like other drugs that affect the renin-angiotensin-aldosterone system, such as ACE inhibitors, may increase blood urea and serum creatinine levels in patients with bilateral or unilateral renal artery stenosis. The same effect may also be seen with angiotensin II receptor antagonists (AIIRA).

Kidney transplantation:
Clinical evidence regarding the use of candesartan cilexetil in patients who have undergone kidney transplantation is limited.

Hypotension:
Hypotension may develop in patients with heart failure treated with CANDEXIL. As with other drugs that affect the renin-angiotensin-aldosterone system, hypotension may also occur in hypertensive patients using high doses of diuretics or with intravascular fluid loss. Caution should be exercised when initiating treatment, and hypovolaemia should be corrected.

Anaesthesia and surgery:
Hypotension may occur during surgery and anaesthesia in patients treated with angiotensin II antagonists due to blockade of the renin-angiotensin system. Very rarely, hypotension may be severe enough to require intravascular fluids and/or vasopressor drugs.

Aortic and mitral valve stenosis or obstructive hypertrophic cardiomyopathy:

As with other vasodilators, CANDEXIL should be used with extreme caution in patients with haemodynamic aortic or mitral valve stenosis or obstructive hypertrophic cardiomyopathy.

Primary hyperaldosteronism:
Patients with primary hyperaldosteronism generally do not respond to antihypertensive drugs that act through the renin-angiotensin-aldosterone system. Therefore, the use of CANDEXIL is not recommended in these patients.

Hyperkalaemia:
Based on experience with other drugs that affect the renin-angiotensin-aldosterone system, the use of CANDEXIL in combination with potassium-sparing diuretics, potassium preparations, artificial salts containing potassium, or other drugs that increase potassium levels (e.g., heparin and trimethoprim/sulfamethoxazole combination) may increase serum potassium levels in hypertensive patients.

Hyperkalaemia may occur in heart failure patients treated with CANDEXIL.

In heart failure patients treated with CANDEXIL, regular monitoring of serum potassium levels is recommended, especially when used in combination with potassium-sparing diuretics such as ACE inhibitors and spironolactone (e.g. spironolactone). The combination of an ACE inhibitor, a potassium-sparing diuretic (e.g. spironolactone) and CANDEXIL is not recommended and should only be considered after careful assessment of the potential benefits and risks.

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

General:
In patients whose renal function and vascular tone depend on the activity of the renin-angiotensin-aldosterone system (e.g. renal diseases including severe congestive heart failure or renal artery stenosis), treatment with other drugs affecting this system is associated with acute hypotension, azotaemia, oliguria, or, rarely, acute renal failure. The possibility of similar effects with AIIRA cannot be excluded. As with any antihypertensive agent, excessive blood pressure reduction in patients with ischaemic heart disease or atherosclerotic cerebrovascular disease may lead to myocardial infarction or stroke.

The antihypertensive effect of candesartan may be increased when used in combination with other drugs that have a blood pressure-lowering effect, whether prescribed as antihypertensives or for other indications.

It should be used with caution in patients who have previously suffered a stroke.

Pregnancy:
Treatment with AIIRA should not be initiated during pregnancy. Unless continued AIIRA therapy is essential, patients planning pregnancy should be switched to other antihypertensive treatments with proven safety in pregnancy. If pregnancy is detected, AIIRA treatment should be discontinued immediately and, where appropriate, alternative treatment should be initiated (see Sections 4.3 and 4.6).

4.5 Interaction with other medicinal products and other forms of interaction
The drugs studied in clinical pharmacokinetic studies were hydrochlorothiazide, warfarin, digoxin, oral contraceptives (e.g. ethinylestradiol/levonorgestrel), glibenclamide, nifedipine, and enalapril. No clinically significant drug interactions were identified when used concomitantly with these drugs.

The use of CANDEXIL with potassium-sparing diuretics, potassium preparations, artificial salts containing potassium, or medicinal products that increase potassium levels (e.g., heparin) may increase serum potassium levels. Potassium levels should be monitored regularly (see Section 4.4).

Reversible increases in serum lithium concentrations and toxicity have been reported with the concomitant use of ACE inhibitors and lithium. A similar effect may occur with AIIRA. The concomitant use of candesartan with lithium is not recommended. If the combination is necessary, careful monitoring of serum lithium levels is advised.

Concomitant use of AIIRA with NSAIDs (non-steroid anti-inflammatory drugs) (e.g. selective COX-2 inhibitors, acetylsalicylic acid (>3 g/day) and non-selective NSAIDs) may cause a reduction in antihypertensive effect and should therefore be used with caution.

As with ACE inhibitors, the combined use of AIIRA and NSAID drugs may cause deterioration of renal function, including possible acute renal failure, and an increase in serum potassium levels (particularly in patients with known pre-existing renal impairment). Particular caution should be exercised when administering combined therapy to elderly patients. Patients should drink sufficient amounts of water, and renal function should be monitored periodically after initiation of combined therapy and thereafter.

Use with alcohol:

Some people who consume alcohol while using CANDEXIL may experience dizziness or lightheadedness. Therefore, alcohol consumption is not recommended while using CANDEXIL.

Clinical trial data have shown that dual blockade of the renin-angiotensin-aldosterone system (RAAS) with 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).

Additional information on specific populations:
No interaction studies have been conducted.

Paediatric population:
The use of candesartan in children under 18 years of age is not recommended due to insufficient data regarding its safety and/or efficacy.

4.6 Pregnancy and lactation
General Recommendation
Pregnancy category: D

Women of childbearing potential/Contraception
Patients who are planning to become pregnant or suspect they may be pregnant should discontinue CANDEXIL use immediately.

Pregnancy
The use of CANDEXIL during pregnancy is contraindicated (see Section 4.3). Patients using CANDEXIL should be reminded of the possibility of becoming pregnant beforehand so that they can determine the appropriate option with their treating physician. When pregnancy is detected, CANDEXIL treatment should be discontinued and, where appropriate, alternative treatment should be initiated.

Medicinal products that directly affect the renin-angiotensin system may cause foetal and neonatal harm and even death when used during pregnancy. Treatment with AIIRA is known to cause foetotoxicity (decreased renal function, oligohydramnios, delayed ossification of the skull) and neonatal toxicity (renal failure, hypotension, hyperkalaemia) (see Section 5.3).

Lactation
It is unknown whether candesartan passes into breast milk. Candesartan has been observed to pass into milk in lactating rats. Due to the potential for adverse effects in breastfed infants, breastfeeding should be discontinued if CANDEXIL use is necessary (see Section 4.3).

Reproductive ability/Fertility
No data available.

4.7 Effects on ability to drive and use machinery
There are no studies on the effect of candesartan on the ability to drive. Drowsiness or fatigue may occur during treatment, so caution should be exercised when driving or using machinery.

4.8 Undesirable effects
In the treatment of hypertension:
In controlled clinical trials, adverse effects were mild and transient and comparable to those seen with placebo. The incidence of side effects was not related to dose or age. The discontinuation rate due to side effects of candesartan cilexetil (3.1%) was similar to that seen with placebo (3.2%).
In the analysis of the total data obtained from clinical trials, the adverse events commonly seen with candesartan are listed below. These adverse events are listed based on the principle of being at least 1% more frequent than with placebo. Accordingly, the most commonly reported side effects are dizziness/vertigo, headache, and respiratory tract infection.
Frequencies 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), not known (cannot be estimated from available data).

Infections and infestations
Common: Respiratory tract infection

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

Metabolic and nutritional disorders
Very rare: Hyperkalaemia, hyponatraemia

Nervous system disorders
Common: Dizziness/vertigo, headache

Respiratory, thoracic and mediastinal disorders
Very rare: Cough

Gastrointestinal disorders
Very rare: Nausea, intestinal angioedema

Hepatobiliary disorders
Very rare: Increased liver enzymes, abnormal hepatic function, or hepatitis

Skin and subcutaneous tissue disorders
Very rare: Angioedema, rash, urticaria, pruritus

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

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

Laboratory Findings:
In general, candesartan cilexetil has no clinically significant effect on routine laboratory findings. As with other inhibitors of the renin-angiotensin-aldosterone system, a slight decrease in haemoglobin levels has been observed. Routine monitoring of laboratory changes is not necessary in patients using CANDEXIL. However, serum potassium and creatinine levels should be monitored regularly in patients with renal impairment.

In the treatment of heart failure:
The side effect profile of candesartan observed in heart failure patients is consistent with the pharmacological effects of the drug and the health status of the patients. In the CHARM clinical trial comparing a 32 mg dose of candesartan (n=3,803) with placebo (n=3,796), 21% of patients in the group receiving candesartan cilexetil discontinued treatment due to adverse effects, compared with 16.1% in the placebo group.

The most commonly reported side effects are hyperkalaemia, hypotension and renal impairment. These effects are more common in individuals over 70 years of age, those with diabetes or other medical drugs affecting the renin-angiotensin-aldosterone system (particularly ACE inhibitors and/or spironolactone).

Side effects obtained from clinical trials and post-marketing experience are listed below:

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

Metabolism and nutrition disorders
Common: Hyperkalaemia
Very rare: Hyponatraemia

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

Hepatobiliary disorders
Very rare: Increased liver enzymes, abnormal hepatic function, or hepatitis

Skin and subcutaneous tissue disorders
Very rare: Angioedema, rash, urticaria, pruritus

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

Kidney and urinary tract disorders
Common: Renal impairment, including renal failure in susceptible patients (see Section 4.4)

Laboratory findings
Hyperkalaemia and renal impairment are commonly observed in the treatment of heart failure with candesartan. Regular monitoring of serum creatinine and potassium levels is recommended (see Section 4.4).

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
Symptoms:
Considering the pharmacological properties, the main findings of overdose may be symptomatic hypotension and dizziness. In individual case reports of overdose (up to 672 mg of candesartan cilexetil), the patient's condition has improved without complications.

Treatment:
If symptomatic hypotension develops, symptomatic treatment should be administered and the patient's vital signs monitored. The patient should be placed in a supine position with the legs elevated. If this is insufficient, plasma volume should be increased by administering a solution

such as physiological saline via infusion. If these measures are also insufficient, sympathomimetic agents may be administered. Candesartan cannot be removed by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Agents that act on the renin-angiotensin system, Angiotensin II receptor blockers
ATC code: C09CA06

Angiotensin II is the most important vasoactive hormone in the renin-angiotensin-aldosterone system and plays a significant role in the pathophysiology 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 secretion, regulation of salt and water balance, and stimulation of cell growth, occur via the type I receptor (AT_1).

Candesartan cilexetil is a prodrug suitable for oral administration. During absorption from the gastrointestinal tract, it is rapidly converted to its active form, candesartan, by ester hydrolysis. Candesartan is an AIIRA that binds selectively and tightly to AT_1 receptors and dissociates slowly. It has no agonist activity.

Candesartan does not inhibit ADE (angiotensin-converting enzyme), which converts angiotensin I to angiotensin II and breaks down bradykinin. It has no effect on bradykinin, substance P, or ACE. In controlled clinical trials comparing ACE inhibitors with candesartan, cough was less common 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. Angiotensin II (AT_1) receptor antagonism causes dose-dependent increases in plasma renin, angiotensin I, and angiotensin II levels, as well as a decrease in plasma aldosterone concentration.

Hypertension

Candesartan exerts its effect in the treatment of hypertension by producing a long-lasting, dose-dependent reduction in arterial blood pressure. Its antihypertensive effect is due to a reduction in systemic peripheral resistance without causing a reflex increase in heart rate. There are no findings of severe hypotension after the first dose or rebound effect after discontinuation of treatment.

Following a single dose of candesartan cilexetil, the antihypertensive effect generally begins within 2 hours. When the drug is used continuously at any dose, most of the reduction in blood

pressure is generally achieved within 4 weeks, and this level of blood pressure is maintained with long-term treatment. According to meta-analyses, increasing the single daily dose from 16 mg to 32 mg has a small average additional effect. Considering individual differences, an effect above average may be expected in some patients. A single daily dose of candesartan cilexetil causes an effective and consistent reduction in blood pressure over 24 hours, with very little difference between trough and peak effects during the dosing interval. The antihypertensive effect and tolerability of candesartan and losartan were compared in two randomised, double-blind studies involving 1,268 patients with mild to moderate hypertension. Blood pressure reduction (systolic/diastolic) with a single daily dose of 32 mg candesartan cilexetil was 13.1/10.5 mmHg, and with a single daily dose of 100 mg losartan potassium it was 10.0/8.7 mmHg (difference in blood pressure reduction 3.1/1.8 mmHg, $p< 0.0001/p<0.0001$).

Candesartan cilexetil produces an additive antihypertensive effect when used in combination with hydrochlorothiazide. Candesartan is well tolerated when used in combination with hydrochlorothiazide or amlodipine.

The marked antihypertensive effect of drugs that block the renin-angiotensin-aldosterone system is less pronounced in black patients (generally a low-renin population) than in non-black patients. This also applies to candesartan. In an open-label clinical trial involving 5,156 patients with diastolic hypertension, the reduction in blood pressure during candesartan treatment was significantly less in black patients than in non-black patients (14.4/10.3 mmHg / 19/12.7 mmHg, $p<0.0001/p<0.0001$).

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

The effects of once-daily 8-16 mg (mean 12 mg) candesartan cilexetil on cardiovascular morbidity and mortality in 4,937 elderly patients (aged 70-89 years; 21% aged 80 years or older) with mild to moderate hypertension were assessed in a randomised clinical trial (SCOPE-Study on Cognition and Prognosis in the Elderly) and followed up for an average of 3.7 years. Additional antihypertensive therapy was added to the candesartan cilexetil or placebo groups as needed. Blood pressure was reduced from 166/90 mm Hg to 145/80 mm Hg in the candesartan group and from 167/90 mm Hg to 149/82 mm Hg in the control group. No statistically significant difference was observed in the primary endpoint of major cardiovascular events (cardiovascular mortality, non-fatal stroke, and non-fatal myocardial infarction). There were 30 events per 1000 patient years in the control group and 26.7 events in the candesartan group (relative risk 0.89, 95% confidence interval 0.75-1.06, $p=0.19$).

Two large randomised controlled trials (ONTARGET (Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) and VA NEPHRON-D (The Veterans Affairs Nephropathy in Diabetes)) investigated the combined use of an ACE inhibitor with an ARB.

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

These studies did not show any significant benefit on renal and/or cardiovascular endpoints and mortality; compared to monotherapy, an increased risk of hyperkalaemia, acute kidney injury and/or hypotension was observed. Given their similar pharmacodynamic properties, these results are also relevant for other ACE inhibitors and AIIRBs.

Therefore, ACE inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

The ALTITUDE (Aliskiren Trial in Type 2 Diabetes using Cardiovascular and Renal Disease Endpoints) study was designed to test the benefit of adding aliskiren to standard ACE inhibitor or AIIRA therapy in patients with type 2 diabetes mellitus who also had chronic kidney disease, cardiovascular disease, or both. The study was terminated early due to an increased risk of adverse outcomes. In the aliskiren group, both cardiovascular death and stroke were numerically more frequent than in the placebo group, and related adverse events and serious adverse events (hyperkalaemia, hypotension, and renal dysfunction) were reported more frequently in the aliskiren group than in the placebo group.

Heart failure
As seen in the Candesartan in Heart Failure-Assessment of Reduction in Mortality and Morbidity (CHARM) programme, treatment with candesartan cilexetil reduces mortality and heart failure-related hospitalisation and improves symptoms in patients with impaired left ventricular systolic function.

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

Patients receiving optimal chronic heart failure therapy at baseline were randomised to receive placebo or candesartan cilexetil (titrated to a single daily dose of 32 mg or the highest tolerated dose, starting with 4 mg or 8 mg daily, with a mean dose of 24 mg) and followed for a mean of

37.7 months. After 6 months of treatment, 63% of patients continuing candesartan cilexetil (89%) were receiving the target dose of 32 mg.

In the CHARM-Alternatives trial, the composite endpoint of cardiovascular mortality or first hospitalisation for 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 is equivalent to a 23% relative risk reduction. To prevent one patient from dying from a cardiovascular event or being hospitalised for heart failure treatment, 14 patients needed to be treated throughout the study.

A significant reduction was observed with candesartan at the composite endpoint of all-cause mortality or first hospitalisation due to chronic heart failure (relative risk (hazard ratio) 0.8, 95% confidence interval 0.7-0.92, p=0.001). The components of the composite endpoint, mortality and morbidity (hospitalisation due to chronic heart failure), contributed to the positive effect of candesartan. Treatment with candesartan cilexetil resulted in an improvement in NYHA functional class (p=0.008).

In the CHARM-Extended Study, there was a significant reduction in the composite endpoint of cardiovascular mortality or first hospitalisation due to chronic heart failure with candesartan compared to placebo (relative risk (hazard ratio) 0.85, 95% confidence interval 0.75-0.96, p=0.011). This is equivalent to a 15% relative risk reduction. Twenty-three patients needed to be treated throughout the study to prevent one patient from dying from a cardiovascular event or being hospitalised for heart failure.

There was a significant reduction with candesartan in the composite endpoint of all-cause mortality or first hospitalisation for chronic heart failure (relative risk (hazard ratio) 0.87, 95% confidence interval 0.78-0.98, 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 an improvement in NYHA functional class (p=0.02).

In the CHARM-Protected Study, no statistically significant reduction was achieved in the composite endpoint of cardiovascular mortality or first hospitalisation due to chronic heart failure (relative risk (hazard ratio) 0.89, 95% confidence interval 0.77-1.03, p=0.118).

When each of the three CHARM studies was evaluated separately, all-cause mortality was not statistically significant. However, all-cause mortality was also evaluated using the pooled data from the patient groups. CHARM-Alternative and CHARM-Addition (relative risk (hazard ratio) 0.88, 95% confidence interval 0.79-0.98, p=0.018) and the sum of the three studies (hazard ratio 0.91, 95% confidence interval 0.83-1, p=0.055).

The beneficial effects of candesartan on cardiovascular mortality and hospitalisation due to chronic heart failure are the same in all patients, regardless of age, gender, and combination

therapy. Candesartan is also effective in patients receiving a beta-blocker and an ACE inhibitor concomitantly, and this effect is obtained regardless of whether the patient is taking 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 reduces systemic vascular resistance and pulmonary capillary wedge pressure, increases plasma renin activity and angiotensin II concentration, and decreases aldosterone levels.

5.2. Pharmacokinetic properties

Absorption:

Following oral administration, candesartan cilexetil is converted to candesartan, the active form of the drug. The absolute bioavailability of candesartan following oral administration of candesartan cilexetil solution is approximately 40%. The relative bioavailability of the tablet form compared to the same oral solution is approximately 34%, with very little variability. Therefore, the estimated absolute bioavailability of the tablet is 14%. After tablet administration, peak serum concentration (C_{max}) is reached in 3-4 hours. Within the therapeutic dose range, the serum concentration of candesartan increases linearly with increasing doses of the drug. No gender-related differences in the pharmacokinetic properties of candesartan have been observed. The area under the serum concentration-time curve (AUC) of candesartan is not significantly affected by food intake.
The bioavailability of candesartan is not affected by meals.

Distribution:

Candesartan binds extensively to plasma proteins (more than 99%). The plasma distribution volume of candesartan is 0.1 L/kg.

Biotransformation:

Current interaction studies have shown that candesartan has no effect on CYP2C9 and CYP3A4. Based on *in vitro* data, no *in vivo* interaction between candesartan and medicinal products metabolised by cytochrome P450 isoenzymes (CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4) is expected.

Elimination:

The terminal half-life of candesartan is approximately 9 hours. It does not accumulate after repeated doses.

The total plasma clearance of candesartan is approximately 0.37 mL/min/kg, and the renal clearance is approximately 0.19 mL/min/kg. Renal elimination of candesartan occurs via both glomerular filtration and active tubular secretion. Following oral administration of candesartan cilexetil labelled with ^{14}C, approximately 26% of the dose is excreted in the urine as

candesartan, 7% as inactive metabolites, approximately 56% in the faeces as candesartan, and 10% as inactive metabolites.

Linearity/non-linearity:
Within the therapeutic dose range, serum concentration of candesartan increases linearly when the dose of the drug is increased.

Characteristic in patients:
Pharmacokinetics in special populations:
I0n elderly patients (aged 65 years and over),the C_{max} and AUC values of candesartan were found to be 50% and 80% higher, respectively, compared to younger patients. However, the effect on blood pressure and adverse effects after candesartan administration are the same in elderly and younger patients (see Section 4.2).

In patients with mild to moderate renal impairment, C_{max} and AUC values of candesartan increased by approximately 50% and 70%, respectively, during repeated doses, but there was no change in $t_{1/2}$values compared to those with normal renal function. Similar changes in patients with severe renal impairment were approximately 50% and 110%, respectively. The half-life of candesartan is approximately doubled in patients with severe renal impairment. The pharmacokinetics in patients undergoing haemodialysis are similar to those in patients with severe renal impairment.

In two clinical studies involving patients with mild and moderate hepatic impairment, the increase in the mean AUC value for candesartan was approximately 20% in one study and 80% in the other (see Section 4.2). There is no experience in patients with severe hepatic impairment.

5.3. Preclinical safety data
No abnormal systemic or target organ toxicity was observed when administered at clinically appropriate doses. In preclinical safety studies, high doses of candesartan administered to mice, rats, dogs, and monkeys were found to affect renal and red blood cell parameters. Candesartan caused a decrease in red blood cell values (erythrocytes, haemoglobin, haematocrit). The effects on the kidneys (interstitial nephritis, tubular distension, basophilic tubules; increased plasma urea and creatinine concentrations) were attributable to candesartan and may be secondary to its hypotensive effect, which leads to changes in renal perfusion. Furthermore, candesartan caused hyperplasia/hypertrophy in juxtaglomerular cells. These changes are thought to be due to the pharmacological effect of candesartan. In humans, no association between candesartan used at therapeutic doses and hyperplasia/hypertrophy in renal juxtaglomerular cells has been observed.
In preclinical studies with normotensive and juvenile rats, candesartan caused a decrease in body weight and heart weight. In adult animals, these effects are thought to be due to the pharmacological effect of candesartan. Exposure to candesartan at the lowest dose of 10 mg/kg

was 12 to 78 times higher than the levels detected in children aged 1 to <6 years who received 0.2 mg/kg candesartan cilexetil and 7 to 54 times higher than the levels detected in children aged 6 to <17 years who received 16 mg candesartan cilexetil. As no effect was observed at the levels detected in these studies, the safety margin regarding effects on heart weight and the clinical significance of the findings are unknown.

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

In vitro and *in vivo* mutagenicity tests have indicated that candesartan has no mutagenic or clastogenic effects in clinical use.

There is no evidence of carcinogenicity.

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

Blockade of the renin-angiotensin-aldosterone system has been shown to cause abnormal kidney development in very young mice. Administration of drugs that directly affect the renin-angiotensin-aldosterone system may alter normal renal development. Therefore, CANDEXIL should not be administered to children under 1 year of age (see Section 4.3).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol
Maize Starch
Red Iron Oxide (E172)
Microcrystalline Cellulose PH 102
Copovidone
Glycerol
Magnesium Stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Should be stored at room temperature below 25°C.

6.5 Nature and contents of container

Our product's primary packaging material is PVC-PVDC foil/aluminium foil blister packs. Each box contains blister packs with 28 tablets, accompanied by a package leaflet.

6.6 Special precautions for disposal and other handling

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

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER(S)

2017/206

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorization : 05.04.2017
Date of latest renewal :

10. DATE OF REVISION OF THE TEXT