COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Candesartan cilexetil Krka 4 mg, 8 mg, 16 mg and 32 mg tablets (candesartan cilexetil)

NL/H/4637/001-004/DC

Date: 2 March 2023

This module reflects the scientific discussion for the approval of Candesartan cilexetil Krka 4 mg, 8 mg, 16 mg and 32 mg tablets. The procedure was finalised in the United Kingdom (UK/H/4626/001-004/DC). After a transfer in 2018, the current RMS is the Netherlands. The report presented below reflects the original procedure at the time of finalisation in the UK and has not been changed or updated since.

Safeguarding public health

MHRA

Public Assessment Report

Decentralised Procedure

CANDESARTAN CILEXETIL 4 MG, 8 MG, 16 MG AND 32 MG TABLETS

CANDESARTAN CILEXETIL

UK/H/4347 & 4626/001-4/DC

UK Licence No: PL 35084/0002-9

MIKLICH LABORATORIOS S.L.

LAY SUMMARY

On 12th March 2012, the UK granted Miklich Laboratorios S.L. Marketing Authorisations (licences) for Candesartan cilexetil 4 mg, 8 mg, 16 mg and 32 mg tablets.

Candesartan cilexetil 4 mg, 8 mg, 16 mg and 32 mg tablets contain the active ingredient, candesartan cilexetil, which belongs to a group of medicines called angiotensin II receptor antagonists. It works by making your blood vessels relax and widen. This helps to lower your blood pressure. It also makes it easier for your heart to pump blood to all parts of your body.

Candesartan cilexetil 4 mg, 8 mg, 16 mg and 32 mg tablets are used for:
• treating high blood pressure (hypertension) in adult patients.
• treating adult heart failure patients with reduced heart muscle function, in addition to Angiotensin Converting Enzyme (ACE) inhibitors or when ACE inhibitors cannot be used (ACE inhibitors are a group of medicines used to treat heart failure).

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Candesartan cilexetil 4 mg, 8 mg, 16 mg and 32 mg tablets outweigh the risks; hence these Marketing Authorisations have been granted.

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Module 1

Product Name	Candesartan cilexetil 4 mg Tablets Candesartan cilexetil 8 mg Tablets Candesartan cilexetil 16 mg Tablets Candesartan cilexetil 32 mg Tablets
Type of Application	Generic application, Article 10.1
Active Substance	Candesartan cilexetil
Form	Tablets
Strength	4 mg 8 mg 16 mg 32 mg
MA Holder	Miklich Laboratorios S.L., Cuevas bajas, s/n - Of.23, Edificio Picasso, 29004 Malaga, Spain.
Reference Member State (RMS)	United Kingdom (UK)
Concerned Member States (CMS)	UK/H/4347/001-4/DC: Austria (AT), Belgium (BE), Cyprus (CY), Germany (DE), Denmark (DK), Greece (EL), Spain (ES), Finland (FI), France (FR), Hungary (HU), Ireland (IE), Italy (IT), the Netherlands (NL), Norway (NO), Portugal (PT) and Sweden (SE) UK/H/4626/001-4/DC: Germany (DE), Spain (ES), France (FR), Italy (IT) and the Netherlands (NL)
Procedure Number	UK/H/4347/001/DC UK/H/4347/002/DC UK/H/4347/003/DC UK/H/4347/004/DC UK/H/4626/001/DC UK/H/4626/002/DC UK/H/4626/003/DC UK/H/4626/004/DC
End of Procedure	Day 200: 9th February 2012

Module 2
Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Candesartan cilexetil 4 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 4 mg candesartan cilexetil.

Excipient:

	4 mg tablets
Lactose monohydrate	94.050 mg

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Tablet.
4 mg: Round, white, biconvex, one side scored tablets.
The scoreline is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Treatment of essential hypertension in adults.
Treatment of adult patients with heart failure and impaired left ventricular systolic function (left ventricular ejection fraction ≤ 40%) as add-on therapy to Angiotensin Converting Enzyme (ACE) inhibitors or when ACE inhibitors are not tolerated (see section 5.1).

4.2 Posology and method of administration
Posology in hypertension
The recommended initial dose and usual maintenance dose of Candesartan cilexetil is 8 mg once daily. Most of the antihypertensive effect is attained within 4 weeks. In some patients whose blood pressure is not adequately controlled, the dose can be increased to 16 mg once daily and to a maximum of 32 mg once daily. Therapy should be adjusted according to blood pressure response.
Candesartan cilexetil may also be administered with other antihypertensive agents. Addition of hydrochlorothiazide has been shown to have an additive antihypertensive effect with various doses of Candesartan cilexetil.

Elderly population
No initial dosage adjustment is necessary in elderly patients.

Patients with intravascular volume depletion
An initial dose of 4 mg may be considered in patients at risk for hypotension, such as patients with possible volume depletion (see section 4.4).

Patients with renal impairment
The starting dose is 4 mg in patients with renal impairment, including patients on haemodialysis. The dose should be titrated according to response. There is limited experience in patients with very severe or end-stage renal impairment ($Cl_{creatinine}$ <15 ml/min) (see section 4.4).

Patients with hepatic impairment
An initial dose of 4 mg once daily is recommended in patients with mild to moderate hepatic impairment. The dose may be adjusted according to response. Candesartan cilexetil is contraindicated in patients with severe hepatic impairment and/or cholestasis (see sections 4.3 and 5.2).

Black patients
The antihypertensive effect of candesartan is less pronounced in black patients than in non-black patients. Consequently, uptitration of Candesartan cilexetil and concomitant therapy may be more frequently needed for blood pressure control in black than non-black patients (see section 5.1).

Posology in heart failure
The usual recommended initial dose of Candesartan cilexetil is 4 mg once daily. Up-titration to the target dose of 32 mg once daily (maximum dose) or the highest tolerated dose is done by doubling the dose at intervals of at least 2 weeks (see section 4.4). Evaluation of patients with heart failure should always comprise assessment of renal function including monitoring of serum creatinine and potassium. Candesartan cilexetil can be administered with other heart failure treatment, including ACE inhibitors, beta-blockers, diuretics and digitalis or a combination of these medicinal products. The combination of an ACE inhibitor, a potassium-sparing diuretic (e.g. spironolactone) and Candesartan cilexetil is not recommended and should be considered only after careful evaluation of the potential benefits and risks (see sections 4.4, 4.8 and 5.1).

Special patient populations
No initial dose adjustment is necessary for elderly patients or in patients with intravascular volume depletion, renal impairment or mild to moderate hepatic impairment.

Paediatric population
The safety and efficacy of Candesartan cilexetil in children aged between birth and 18 years have not been established in the treatment of hypertension and heart failure. No data are available.

Method of administration
Oral use.
Candesartan cilexetil should be taken once daily with or without food.
The bioavailability of candesartan is not affected by food.

4.3 Contraindications
Hypersensitivity to the active substance or to any of the excipients.
Second and third trimester of pregnancy (see sections 4.4 and 4.6).
Severe hepatic impairment and/or cholestasis.

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 Candesartan cilexetil.
When Candesartan cilexetil is used in hypertensive patients with renal impairment, periodic monitoring of serum potassium and creatinine levels is recommended. There is limited experience in patients with very severe or end-stage renal impairment ($Cl_{creatinine}$ < 15 ml/min). In these patients Candesartan cilexetil should be carefully titrated with thorough monitoring of blood pressure.
Evaluation of patients with heart failure should include periodic assessments of renal function, especially in elderly patients 75 years or older, and patients with impaired renal function. During dose titration of Candesartan cilexetil, 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).

Concomitant therapy with an ACE inhibitor in heart failure
The risk of adverse reactions, especially renal function impairment and hyperkalaemia, may increase when candesartan is used in combination with an ACE inhibitor (see section 4.8). Patients with such treatment should be monitored regularly and carefully.

Haemodialysis
During dialysis the blood pressure may be particularly sensitive to AT_1-receptor blockade as a result of reduced plasma volume and activation of the renin-angiotensin-aldosterone system. Therefore Candesartan cilexetil should be carefully titrated with thorough monitoring of blood pressure in patients on haemodialysis.

Renal artery stenosis
Medicinal products that affect the renin-angiotensin-aldosterone system, including angiotensin II receptor antagonists (AIIRAs), may increase blood urea and serum creatinine in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney.

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

Hypotension
Hypotension may occur during treatment with Candesartan cilexetil in heart failure patients. It 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.

Anaesthesia and surgery
Hypotension may occur during anaesthesia and surgery in patients treated with angiotensin II antagonists due to blockade of the renin-angiotensin system. Very rarely, hypotension may be severe such that it may warrant the use of intravenous fluids and/or vasopressors.

Aortic and mitral valve stenosis (obstructive hypertrophic cardiomyopathy)
As with other vasodilators, special caution is indicated in patients suffering from haemodynamically relevant aortic or mitral valve stenosis, or obstructive hypertrophic cardiomyopathy.

Primary hyperaldosteronism
Patients with primary hyperaldosteronism will not generally respond to antihypertensive medicinal products acting through inhibition of the renin-angiotensin-aldosterone system. Therefore, the use of Candesartan cilexetil is not recommended.

Hyperkalaemia
Concomitant use of Candesartan cilexetil with potassium-sparing diuretics, potassium supplements, salt substitutes 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 treated with Candesartan cilexetil, hyperkalaemia may occur. Periodic monitoring of serum potassium is recommended. The combination of an ACE inhibitor, a potassium-sparing diuretic (e.g. spironolactone) and Candesartan cilexetil 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 ischaemic cardiopathy or ischaemic 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.

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 angiotensin II receptor antagonists should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

This medicinal product contains Lactose monohydrate.
Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction
Compounds which have been investigated in clinical pharmacokinetic studies include hydrochlorothiazide, warfarin, digoxin, oral contraceptives (i.e. ethinylestradiol/ levonorgestrel), glibenclamide, nifedipine and enalapril. No clinically significant pharmacokinetic interactions with these medicinal products have been identified.

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

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

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.

4.6 Fertility, pregnancy and lactation

Pregnancy

The use of AIIRAs is not recommended during the first trimester of pregnancy (see section 4.4).The use of AIIRAs is contraindicated during the second and third trimesters of pregnancy (see sections 4.3 and 4.4).

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Whilst there are no controlled epidemiological data on the risk with AIIRAs, similar risks may exist for this class of drug. Unless continued AIIRA therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with AIIRAs should be stopped immediately, and, if appropriate, alternative therapy should be started.

Exposure to AIIRA therapy during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia) (See section 5.3).
Should exposure to AIIRAs have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.
Infants whose mothers have taken AIIRAs should be closely observed for hypotension (see sections 4.3 and 4.4).

Lactation

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

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. However, it should be taken into account that occasionally dizziness or weariness may occur during treatment with Candesartan cilexetil.

4.8 Undesirable effects

Treatment of hypertension

In controlled clinical studies adverse reactions were mild and transient. The overall incidence of adverse events showed no association with dose or age. Withdrawals from treatment due to adverse events were similar with candesartan cilexetil (3.1%) and placebo (3.2%).

In a pooled analysis of clinical trial data of hypertensive patients, the following 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. By this definition, the most commonly reported adverse reactions were dizziness/vertigo, headache and respiratory infection.

The table below presents adverse reactions from clinical trials and post-marketing experience.

The frequencies used in the tables throughout 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)

System Organ Class	Frequency	Undesirable Effect
Infections and infestations	Common	Respiratory infection
Blood and lymphatic system disorders	Very rare	Leukopenia, neutropenia and agranulocytosis
Metabolism and nutrition disorders	Very rare	Hyperkalaemia, hyponatraemia
Nervous system disorders	Common	Dizziness/vertigo, headache
Gastrointestinal disorders	Very rare	Nausea
Hepato-biliary disorders	Very rare	Increased liver enzymes, abnormal hepatic function or hepatitis
Skin and subcutaneous tissue disorders	Very rare	Angioedema, rash, urticaria, pruritus
Musculoskeletal and connective tissue disorders	Very rare	Back pain, arthralgia, myalgia
Renal and urinary disorders	Very rare	Renal impairment, including renal failure in susceptible patients (see section 4.4)

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

Treatment of heart failure
The adverse experience 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 programme, comparing candesartan cilexetil in doses up to 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 hyperkalaemia, 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 table below presents adverse reactions from clinical trials and post-marketing experience.

System Organ Class	Frequency	Undesirable Effect
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
Gastrointestinal disorders	Very rare	Nausea
Hepato-biliary disorders	Very rare	Increased liver enzymes, abnormal hepatic function or hepatitis
Skin and subcutaneous tissue disorders	Very rare	Angioedema, rash, urticaria, pruritus
Musculoskeletal and connective tissue disorders	Very rare	Back pain, arthralgia, myalgia
Renal and urinary disorders	Common	Renal impairment, including renal failure in susceptible patients (see section 4.4)

Laboratory findings
Hyperkalaemia and renal impairment are common in patients treated with Candesartan cilexetil for the indication of heart failure. Periodic monitoring of serum creatinine and potassium is recommended (see section 4.4).

4.9 Overdose

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

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Angiotensin II antagonists, plain, ATC code: C09CA06.

Angiotensin II is the primary vasoactive hormone of the renin-angiotensin-aldosterone system and plays a role in the pathophysiology of hypertension, heart failure and other cardiovascular disorders. It also has a role in the pathogenesis of end organ hypertrophy and damage. The major physiological effects of angiotensin II, such as vasoconstriction, aldosterone stimulation, regulation of salt and water homeostasis and stimulation of cell growth, are mediated via the type 1 (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, selective for AT_1 receptors, with tight binding to and slow dissociation from the receptor. It has no agonist activity.

Candesartan does not inhibit ACE, which converts angiotensin I to angiotensin II and degrades bradykinin. There is no effect on ACE and no potentiation of bradykinin or substance P. In controlled clinical trials comparing candesartan with ACE inhibitors, the incidence of cough was lower in patients receiving candesartan cilexetil. Candesartan does not bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation. The antagonism of the angiotensin II (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 indication of serious or exaggerated first dose hypotension or rebound effect after cessation of treatment.

After administration of a single dose of candesartan cilexetil, onset of antihypertensive effect generally occurs within 2 hours. With continuous treatment, most of the reduction in blood pressure with any dose is generally attained within four weeks and is sustained during long-term treatment. According to a meta-analysis, the average additional effect of a dose increase from 16 mg to 32 mg once daily was small. Taking into account the inter-individual variability, a more than average effect can be expected in some patients. Candesartan cilexetil once daily provides effective and smooth blood pressure reduction over 24 hours with little difference between maximum and trough effects during the dosing interval. The antihypertensive effect and tolerability of candesartan and losartan were compared in two randomised, double-blind studies in a total of 1,268 patients with mild to moderate hypertension. The trough blood pressure reduction (systolic/diastolic) was 13.1/10.5 mmHg with candesartan cilexetil 32 mg once daily and 10.0/8.7 mmHg with losartan potassium 100 mg once daily (difference in blood pressure reduction 3.1/1.8 mmHg, $p<0.0001/p<0.0001$).

When candesartan cilexetil is used together with hydrochlorothiazide, the reduction in blood pressure is additive. An increased antihypertensive effect is also seen when candesartan cilexetil is combined with amlodipine or felodipine. Medicinal products that block the renin-angiotensin-aldosterone system have less pronounced antihypertensive effect in black patients (usually a low-renin population) than in non-black patients. This is also the case for candesartan. In an open-label clinical experience trial in 5,156 patients with diastolic hypertension, the blood pressure reduction during candesartan treatment was significantly less in black than non-black patients (14.4/10.3 mmHg vs 19.0/12.7 mmHg, $p<0.0001/p<0.0001$).

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

The effects of candesartan cilexetil 8-16 mg (mean dose 12 mg) once daily, on cardiovascular morbidity and mortality were evaluated in a randomised clinical trial with 4,937 elderly patients (aged 70-89 years; 21% aged 80 or above) with mild to moderate hypertension followed for a mean of 3.7 years (Study on Cognition and Prognosis in the Elderly). Patients received candesartan cilexetil or placebo with other antihypertensive treatment added as needed. The blood pressure was reduced from 166/90 to 145/80 mmHg in the candesartan group, and from 167/90 to 149/82mmHg 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).

Heart failure

Treatment with candesartan cilexetil reduces mortality, reduces hospitalisation 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) programme.
This placebo controlled, double-blind study programme in chronic heart failure (CHF) patients with NYHA functional class II to IV consisted of three separate studies: CHARM-Alternative (n=2,028) in patients with LVEF ≤ 40% not treated with an ACE inhibitor because of intolerance (mainly due to cough, 72%), CHARM-Added (n=2,548) in patients with LVEF ≤ 40% and treated with an ACE inhibitor, and CHARM-Preserved (n=3,023) in patients with LVEF > 40%. Patients on optimal CHF therapy at baseline were randomised to placebo or candesartan cilexetil (titrated from 4 mg or 8 mg once daily to 32 mg once daily or the highest tolerated dose, mean dose 24 mg) and followed for a median 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 CHARM-Alternative, the composite endpoint of cardiovascular mortality or first CHF hospitalisation was significantly reduced with candesartan in comparison with placebo (hazard ratio (HR) 0.77, 95% CI 0.67-0.89, $p<0.001$). This corresponds to a relative risk reduction of 23%. Of candesartan patients 33.0% (95%CI: 30.1 to 36.0) and of placebo patients 40.0% (95%CI: 37.0 to 43.1) experienced this endpoint, absolute difference 7.0% (95%CI: 11.2 to 2.8). Fourteen patients needed to be treated for the duration of the study to prevent one patient from dying of a cardiovascular event or being hospitalised for treatment of heart failure. The composite endpoint of all-cause mortality or first CHF hospitalisation was also significantly reduced with candesartan HR 0.80 (95% CI0.70-0.92,

p=0.001). Of candesartan patients 36.6% (95%CI: 33.7 to 39.7) and of placebo patients 42.7% (95%CI: 39.6 to 45.8) experienced this endpoint, absolute difference 6.0% (95%CI: 10.3 to 1.8). Both the mortality and morbidity (CHF hospitalisation) components of these composite endpoints contributed to the favourable effects of candesartan. Treatment with candesartan cilexetil resulted in improved NYHA functional class (p=0.008).

In CHARM-Added, the composite endpoint of cardiovascular mortality or first CHF hospitalisation was significantly reduced with candesartan in comparison with placebo HR 0.85 (95%CI 0.75-0.96, p=0.011). This corresponds to a relative risk reduction of 15%. Of candesartan patients 37.9% (95%CI: 35.2 to 40.6) and of placebo patients 42.3% (95%CI: 39.6 to 45.1) experienced this endpoint, absolute difference 4.4% (95%CI: 8.2 to 0.6). Twenty-three patients needed to be treated for the duration of the study to prevent one patient from dying of a cardiovascular event or being hospitalised for treatment of heart failure. The composite endpoint of all-cause mortality or first CHF hospitalisation was also significantly reduced with candesartan HR 0.87 (95%CI 0.78-0.98, p=0.021). Of candesartan patients 42.2% (95%CI: 39.5 to 45.0) and of placebo patients 46.1% (95%CI: 43.4 to 48.9) experienced this endpoint, absolute difference 3.9% (95%CI: 7.8 to 0.1). Both the mortality and morbidity components of these composite endpoints contributed to the favourable effects of candesartan. Treatment with candesartan cilexetil resulted in improved NYHA functional class (p=0.020).

In CHARM-Preserved, no statistically significant reduction was achieved in the composite endpoint of cardiovascular mortality or first CHF hospitalisation, HR 0.89, 95%CI 0.77-1.03, 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, HR 0.88, (95% CI 0.79-0.98, p=0.018) and all three studies HR 0.91 (95%CI 0.83-1.00, p=0.055).

The beneficial effects of candesartan were consistent irrespective of age, gender and concomitant medication. Candesartan was effective also in patients taking both beta-blockers and ACE inhibitors at the same time, and the benefit was obtained whether or not patients were taking ACE inhibitors at the target dose recommended by treatment guidelines.
In patients with CHF and depressed left ventricular systolic function (left ventricular ejection fraction, LVEF $\leq$ 40%), candesartan decreases 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 and distribution

Following oral administration, candesartan cilexetil is converted to the active substance candesartan. The absolute bioavailability of candesartan is approximately 40% after an oral solution of candesartan cilexetil. The relative bioavailability of the tablet formulation compared with the same oral solution is approximately 34% with very little variability. The estimated absolute bioavailability of the tablet is therefore 14%. 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.
Candesartan is highly bound to plasma protein (more than 99%). The apparent volume of distribution of candesartan is 0.1 l/kg.
The bioavailability of candesartan is not affected by food.

Biotransformation and elimination

Candesartan is mainly eliminated unchanged via urine and bile and only to a minor extent eliminated by hepatic metabolism (CYP2C9). Available interaction studies indicate no effect on CYP2C9 and CYP3A4. Based on *in vitro* data, no interaction would be expected to occur *in vivo* with drugs whose metabolism is dependent upon cytochrome P450 isoenzymes CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1 or CYP3A4. The terminal half-life of candesartan is approximately 9 hours. There is no accumulation following multiple doses.
Total plasma clearance of candesartan is about 0.37 ml/min/kg, with a renal clearance of about 0.19 ml/min/kg. The renal elimination of candesartan is both by glomerular filtration and active tubular secretion. Following an oral dose of ^{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 faeces as candesartan and 10% as the inactive metabolite.

Pharmacokinetics in special populations
In the elderly (over 65 years) C_{max} and AUC of candesartan are increased by approximately 50% and 80%, respectively in comparison to young subjects. However, the blood pressure response and the incidence of adverse events are similar after a given dose of candesartan cilexetil in young and elderly patients (see section 4.2).

In patients with mild to moderate renal impairment C_{max} and AUC of candesartan increased during repeated dosing by approximately 50% and 70%, respectively, but $t_{1/2}$ was not altered, compared to patients with normal renal function. The corresponding changes in patients with severe renal impairment were approximately 50% and 110%, respectively. The terminal $t_{1/2}$ of candesartan was approximately doubled in patients with severe renal impairment. The AUC of candesartan in patients undergoing haemodialysis was similar to that in patients with severe renal impairment.
In two studies, both including patients with mild to moderate hepatic impairment, there was an increase in the mean AUC of candesartan of approximately 20% in one study and 80% in the other study (see section 4.2). There is no experience in patients with severe hepatic impairment.

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, haemoglobin, haematocrit). Effects on the kidneys (such as interstitial nephritis, tubular distension, basophilic tubules; increased plasma concentrations of urea and creatinine) were induced by candesartan which could be secondary to the hypotensive effect leading to alterations of renal perfusion. Furthermore, candesartan induced hyperplasia/hypertrophy of the juxtaglomerular cells. These changes were considered to be caused by the pharmacological action of candesartan. For therapeutic doses of candesartan in humans, the hyperplasia/hypertrophy of the renal juxtaglomerular cells does not seem to have any relevance.
Fetotoxicity has been observed in late pregnancy (see section 4.6).
Data from *in vitro* and *in vivo* mutagenicity testing indicate that candesartan will not 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
Maize starch
Dibutyl sebacate
Sodium laurilsulfate
Hydroxypropylcellulose
Carmellose calcium
Magnesium stearate

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years

6.4 Special precautions for storage
Do not store above 30°C.

6.5 Nature and contents of container
Blister PVC/PVDC/Aluminium
Pack sizes: 7, 10, 14, 28, 30, 50, 56, 60, 84, 90, 98, 100 tablets in a box.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER
Miklich Laboratorios S.L., Cuevas bajas, s/n - Of.23, Edificio Picasso, 29004 Malaga, Spain.

8 MARKETING AUTHORISATION NUMBER(S)
PL 35084/0002 & 6

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
12/03/2012

10 DATE OF REVISION OF THE TEXT
12/03/2012

1 NAME OF THE MEDICINAL PRODUCT

Candesartan cilexetil 8 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 8 mg candesartan cilexetil.
Excipient:

	8 mg tablets
Lactose monohydrate	90.035 mg

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.
8 mg: Round, pinkish-white, biconvex, one side scored tablets.

The scoreline is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of essential hypertension in adults.
Treatment of adult patients with heart failure and impaired left ventricular systolic function (left ventricular ejection fraction ≤ 40%) as add-on therapy to Angiotensin Converting Enzyme (ACE) inhibitors or when ACE inhibitors are not tolerated (see section 5.1).

4.2 Posology and method of administration

Posology in hypertension
The recommended initial dose and usual maintenance dose of Candesartan cilexetil is 8 mg once daily. Most of the antihypertensive effect is attained within 4 weeks. In some patients whose blood pressure is not adequately controlled, the dose can be increased to 16 mg once daily and to a maximum of 32 mg once daily. Therapy should be adjusted according to blood pressure response.
Candesartan cilexetil may also be administered with other antihypertensive agents. Addition of hydrochlorothiazide has been shown to have an additive antihypertensive effect with various doses of Candesartan cilexetil.

Elderly population
No initial dosage adjustment is necessary in elderly patients.

Patients with intravascular volume depletion
An initial dose of 4 mg may be considered in patients at risk for hypotension, such as patients with possible volume depletion (see section 4.4).

Patients with renal impairment
The starting dose is 4 mg in patients with renal impairment, including patients on haemodialysis. The dose should be titrated according to response. There is limited experience in patients with very severe or end-stage renal impairment ($Cl_{creatinine}$ <15 ml/min) (see section 4.4).

Patients with hepatic impairment
An initial dose of 4 mg once daily is recommended in patients with mild to moderate hepatic impairment. The dose may be adjusted according to response. Candesartan cilexetil is contraindicated in patients with severe hepatic impairment and/or cholestasis (see sections 4.3 and 5.2).

Black patients
The antihypertensive effect of candesartan is less pronounced in black patients than in non-black patients. Consequently, uptitration of Candesartan cilexetil and concomitant therapy may be more frequently needed for blood pressure control in black than non-black patients (see section 5.1).

Posology in heart failure
The usual recommended initial dose of Candesartan cilexetil is 4 mg once daily. Up-titration to the target dose of 32 mg once daily (maximum dose) or the highest tolerated dose is done by doubling the dose at intervals of at least 2 weeks (see section 4.4). Evaluation of patients with heart failure should always comprise assessment of renal function including monitoring of serum creatinine and potassium. Candesartan cilexetil can be administered with other heart failure treatment, including ACE inhibitors,

beta-blockers, diuretics and digitalis or a combination of these medicinal products. The combination of an ACE inhibitor, a potassium-sparing diuretic (e.g. spironolactone) and Candesartan cilexetil is not recommended and should be considered only after careful evaluation of the potential benefits and risks (see sections 4.4, 4.8 and 5.1).

Special patient populations
No initial dose adjustment is necessary for elderly patients or in patients with intravascular volume depletion, renal impairment or mild to moderate hepatic impairment.

Paediatric population
The safety and efficacy of Candesartan cilexetil in children aged between birth and 18 years have not been established in the treatment of hypertension and heart failure. No data are available.

Method of administration
Oral use.
Candesartan cilexetil should be taken once daily with or without food.
The bioavailability of candesartan is not affected by food.

4.3 Contraindications
Hypersensitivity to the active substance or to any of the excipients.
Second and third trimester of pregnancy (see sections 4.4 and 4.6).
Severe hepatic impairment and/or cholestasis.

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 Candesartan cilexetil.
When Candesartan cilexetil is used in hypertensive patients with renal impairment, periodic monitoring of serum potassium and creatinine levels is recommended. There is limited experience in patients with very severe or end-stage renal impairment ($Cl_{creatinine}$ < 15 ml/min). In these patients Candesartan cilexetil should be carefully titrated with thorough monitoring of blood pressure.
Evaluation of patients with heart failure should include periodic assessments of renal function, especially in elderly patients 75 years or older, and patients with impaired renal function. During dose titration of Candesartan cilexetil, 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).

Concomitant therapy with an ACE inhibitor in heart failure
The risk of adverse reactions, especially renal function impairment and hyperkalaemia, may increase when candesartan is used in combination with an ACE inhibitor (see section 4.8). Patients with such treatment should be monitored regularly and carefully.

Haemodialysis
During dialysis the blood pressure may be particularly sensitive to AT_1-receptor blockade as a result of reduced plasma volume and activation of the renin-angiotensin-aldosterone system. Therefore Candesartan cilexetil should be carefully titrated with thorough monitoring of blood pressure in patients on haemodialysis.

Renal artery stenosis
Medicinal products that affect the renin-angiotensin-aldosterone system, including angiotensin II receptor antagonists (AIIRAs), may increase blood urea and serum creatinine in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney.

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

Hypotension
Hypotension may occur during treatment with Candesartan cilexetil in heart failure patients. It 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.

Anaesthesia and surgery
Hypotension may occur during anaesthesia and surgery in patients treated with angiotensin II antagonists due to blockade of the renin-angiotensin system. Very rarely, hypotension may be severe such that it may warrant the use of intravenous fluids and/or vasopressors.

Aortic and mitral valve stenosis (obstructive hypertrophic cardiomyopathy)
As with other vasodilators, special caution is indicated in patients suffering from haemodynamically relevant aortic or mitral valve stenosis, or obstructive hypertrophic cardiomyopathy.

Primary hyperaldosteronism
Patients with primary hyperaldosteronism will not generally respond to antihypertensive medicinal products acting through inhibition of the renin-angiotensin-aldosterone system. Therefore, the use of Candesartan cilexetil is not recommended.

Hyperkalaemia
Concomitant use of Candesartan cilexetil with potassium-sparing diuretics, potassium supplements, salt substitutes 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 treated with Candesartan cilexetil, hyperkalaemia may occur. Periodic monitoring of serum potassium is recommended. The combination of an ACE inhibitor, a potassium-sparing diuretic (e.g. spironolactone) and Candesartan cilexetil 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 ischaemic cardiopathy or ischaemic 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.

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 angiotensin II receptor antagonists should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

This medicinal product contains Lactose monohydrate.
Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction
Compounds which have been investigated in clinical pharmacokinetic studies include hydrochlorothiazide, warfarin, digoxin, oral contraceptives (i.e. ethinylestradiol/ levonorgestrel), glibenclamide, nifedipine and enalapril. No clinically significant pharmacokinetic interactions with these medicinal products have been identified.

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

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

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.

4.6 Fertility, pregnancy and lactation

Pregnancy

The use of AIIRAs is not recommended during the first trimester of pregnancy (see section 4.4).The use of AIIRAs is contraindicated during the second and third trimesters of pregnancy (see sections 4.3 and 4.4).

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Whilst there are no controlled epidemiological data on the risk with AIIRAs, similar risks may exist for this class of drug. Unless continued AIIRA therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with AIIRAs should be stopped immediately, and, if appropriate, alternative therapy should be started.

Exposure to AIIRA therapy during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia) (See section 5.3).
Should exposure to AIIRAs have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.
Infants whose mothers have taken AIIRAs should be closely observed for hypotension (see sections 4.3 and 4.4).

Lactation

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

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. However, it should be taken into account that occasionally dizziness or weariness may occur during treatment with Candesartan cilexetil.

4.8 Undesirable effects

Treatment of hypertension

In controlled clinical studies adverse reactions were mild and transient. The overall incidence of adverse events showed no association with dose or age. Withdrawals from treatment due to adverse events were similar with candesartan cilexetil (3.1%) and placebo (3.2%).

In a pooled analysis of clinical trial data of hypertensive patients, the following 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. By this definition, the most commonly reported adverse reactions were dizziness/vertigo, headache and respiratory infection.

The table below presents adverse reactions from clinical trials and post-marketing experience.

The frequencies used in the tables throughout 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)

System Organ Class	Frequency	Undesirable Effect
Infections and infestations	Common	Respiratory infection
Blood and lymphatic system disorders	Very rare	Leukopenia, neutropenia and agranulocytosis
Metabolism and nutrition disorders	Very rare	Hyperkalaemia, hyponatraemia
Nervous system disorders	Common	Dizziness/vertigo, headache
Gastrointestinal disorders	Very rare	Nausea
Hepato-biliary disorders	Very rare	Increased liver enzymes, abnormal hepatic function or hepatitis
Skin and subcutaneous tissue disorders	Very rare	Angioedema, rash, urticaria, pruritus
Musculoskeletal and connective tissue disorders	Very rare	Back pain, arthralgia, myalgia
Renal and urinary disorders	Very rare	Renal impairment, including renal failure in susceptible patients (see section 4.4)

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

Treatment of heart failure
The adverse experience 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 programme, comparing candesartan cilexetil in doses up to 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 hyperkalaemia, 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 table below presents adverse reactions from clinical trials and post-marketing experience.

System Organ Class	Frequency	Undesirable Effect
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
Gastrointestinal disorders	Very rare	Nausea
Hepato-biliary disorders	Very rare	Increased liver enzymes, abnormal hepatic function or hepatitis
Skin and subcutaneous tissue	Very rare	Angioedema, rash, urticaria, pruritus

disorders		
Musculoskeletal and connective tissue disorders	Very rare	Back pain, arthralgia, myalgia
Renal and urinary disorders	Common	Renal impairment, including renal failure in susceptible patients (see section 4.4)

Laboratory findings
Hyperkalaemia and renal impairment are common in patients treated with Candesartan cilexetil for the indication of heart failure. Periodic monitoring of serum creatinine and potassium is recommended (see section 4.4).

4.9 Overdose

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

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Angiotensin II antagonists, plain, ATC code: C09CA06.

Angiotensin II is the primary vasoactive hormone of the renin-angiotensin-aldosterone system and plays a role in the pathophysiology of hypertension, heart failure and other cardiovascular disorders. It also has a role in the pathogenesis of end organ hypertrophy and damage. The major physiological effects of angiotensin II, such as vasoconstriction, aldosterone stimulation, regulation of salt and water homeostasis and stimulation of cell growth, are mediated via the type 1 (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, selective for AT_1 receptors, with tight binding to and slow dissociation from the receptor. It has no agonist activity.

Candesartan does not inhibit ACE, which converts angiotensin I to angiotensin II and degrades bradykinin. There is no effect on ACE and no potentiation of bradykinin or substance P. In controlled clinical trials comparing candesartan with ACE inhibitors, the incidence of cough was lower in patients receiving candesartan cilexetil. Candesartan does not bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation. The antagonism of the angiotensin II (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 indication of serious or exaggerated first dose hypotension or rebound effect after cessation of treatment.

After administration of a single dose of candesartan cilexetil, onset of antihypertensive effect generally occurs within 2 hours. With continuous treatment, most of the reduction in blood pressure with any dose is generally attained within four weeks and is sustained during long-term treatment. According to a meta-analysis, the average additional effect of a dose increase from 16 mg to 32 mg once daily was small. Taking into account the inter-individual variability, a more than average effect can be expected in some patients. Candesartan cilexetil once daily provides effective and smooth blood pressure reduction over 24 hours with little difference between maximum and trough effects during the dosing

interval. The antihypertensive effect and tolerability of candesartan and losartan were compared in two randomised, double-blind studies in a total of 1,268 patients with mild to moderate hypertension. The trough blood pressure reduction (systolic/diastolic) was 13.1/10.5 mmHg with candesartan cilexetil 32 mg once daily and 10.0/8.7 mmHg with losartan potassium 100 mg once daily (difference in blood pressure reduction 3.1/1.8 mmHg, $p<0.0001/p<0.0001$).

When candesartan cilexetil is used together with hydrochlorothiazide, the reduction in blood pressure is additive. An increased antihypertensive effect is also seen when candesartan cilexetil is combined with amlodipine or felodipine. Medicinal products that block the renin-angiotensin-aldosterone system have less pronounced antihypertensive effect in black patients (usually a low-renin population) than in non-black patients. This is also the case for candesartan. In an open-label clinical experience trial in 5,156 patients with diastolic hypertension, the blood pressure reduction during candesartan treatment was significantly less in black than non-black patients (14.4/10.3 mmHg vs 19.0/12.7 mmHg, $p<0.0001/p<0.0001$).

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

The effects of candesartan cilexetil 8-16 mg (mean dose 12 mg) once daily, on cardiovascular morbidity and mortality were evaluated in a randomised clinical trial with 4,937 elderly patients (aged 70-89 years; 21% aged 80 or above) with mild to moderate hypertension followed for a mean of 3.7 years (Study on Cognition and Prognosis in the Elderly). Patients received candesartan cilexetil or placebo with other antihypertensive treatment added as needed. The blood pressure was reduced from 166/90 to 145/80 mmHg in the candesartan group, and from 167/90 to 149/82mmHg 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).

Heart failure

Treatment with candesartan cilexetil reduces mortality, reduces hospitalisation 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) programme.
This placebo controlled, double-blind study programme in chronic heart failure (CHF) patients with NYHA functional class II to IV consisted of three separate studies: CHARM-Alternative (n=2,028) in patients with LVEF $\leq$ 40% not treated with an ACE inhibitor because of intolerance (mainly due to cough, 72%), CHARM-Added (n=2,548) in patients with LVEF $\leq$ 40% and treated with an ACE inhibitor, and CHARM-Preserved (n=3,023) in patients with LVEF > 40%. Patients on optimal CHF therapy at baseline were randomised to placebo or candesartan cilexetil (titrated from 4 mg or 8 mg once daily to 32 mg once daily or the highest tolerated dose, mean dose 24 mg) and followed for a median 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 CHARM-Alternative, the composite endpoint of cardiovascular mortality or first CHF hospitalisation was significantly reduced with candesartan in comparison with placebo (hazard ratio (HR) 0.77, 95% CI 0.67-0.89, $p<0.001$). This corresponds to a relative risk reduction of 23%. Of candesartan patients 33.0% (95%CI: 30.1 to 36.0) and of placebo patients 40.0% (95%CI: 37.0 to 43.1) experienced this endpoint, absolute difference 7.0% (95%CI: 11.2 to 2.8). Fourteen patients needed to be treated for the duration of the study to prevent one patient from dying of a cardiovascular event or being hospitalised for treatment of heart failure. The composite endpoint of all-cause mortality or first CHF hospitalisation was also significantly reduced with candesartan HR 0.80 (95% CI0.70-0.92, p=0.001). Of candesartan patients 36.6% (95%CI: 33.7 to 39.7) and of placebo patients 42.7% (95%CI: 39.6 to 45.8) experienced this endpoint, absolute difference 6.0% (95%CI: 10.3 to 1.8). Both the mortality and morbidity (CHF hospitalisation) components of these composite endpoints contributed to the favourable effects of candesartan. Treatment with candesartan cilexetil resulted in improved NYHA functional class (p=0.008).

In CHARM-Added, the composite endpoint of cardiovascular mortality or first CHF hospitalisation was significantly reduced with candesartan in comparison with placebo HR 0.85 (95%CI 0.75-0.96, p=0.011). This corresponds to a relative risk reduction of 15%. Of candesartan patients 37.9% (95%CI: 35.2 to 40.6) and of placebo patients 42.3% (95%CI: 39.6 to 45.1) experienced this endpoint, absolute difference 4.4% (95%CI: 8.2 to 0.6). Twenty-three patients needed to be treated for the duration of the study to prevent one patient from dying of a cardiovascular event or being hospitalised for treatment of heart failure. The composite endpoint of all-cause mortality or first CHF hospitalisation was also significantly reduced with candesartan HR 0.87 (95%CI 0.78-0.98, p=0.021). Of candesartan patients 42.2% (95%CI: 39.5 to 45.0) and of placebo patients 46.1% (95%CI: 43.4 to 48.9) experienced this endpoint, absolute difference 3.9% (95%CI: 7.8 to 0.1). Both the mortality and morbidity components of these composite endpoints contributed to the favourable effects of candesartan. Treatment with candesartan cilexetil resulted in improved NYHA functional class (p=0.020).

In CHARM-Preserved, no statistically significant reduction was achieved in the composite endpoint of cardiovascular mortality or first CHF hospitalisation, HR 0.89, 95%CI 0.77-1.03, 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, HR 0.88, (95% CI 0.79-0.98, p=0.018) and all three studies HR 0.91 (95%CI 0.83-1.00, p=0.055).

The beneficial effects of candesartan were consistent irrespective of age, gender and concomitant medication. Candesartan was effective also in patients taking both beta-blockers and ACE inhibitors at the same time, and the benefit was obtained whether or not patients were taking ACE inhibitors at the target dose recommended by treatment guidelines.
In patients with CHF and depressed left ventricular systolic function (left ventricular ejection fraction, LVEF $\leq$ 40%), candesartan decreases 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 and distribution

Following oral administration, candesartan cilexetil is converted to the active substance candesartan. The absolute bioavailability of candesartan is approximately 40% after an oral solution of candesartan cilexetil. The relative bioavailability of the tablet formulation compared with the same oral solution is approximately 34% with very little variability. The estimated absolute bioavailability of the tablet is therefore 14%. 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.
Candesartan is highly bound to plasma protein (more than 99%). The apparent volume of distribution of candesartan is 0.1 l/kg.
The bioavailability of candesartan is not affected by food.

Biotransformation and elimination

Candesartan is mainly eliminated unchanged via urine and bile and only to a minor extent eliminated by hepatic metabolism (CYP2C9). Available interaction studies indicate no effect on CYP2C9 and CYP3A4. Based on *in vitro* data, no interaction would be expected to occur *in vivo* with drugs whose metabolism is dependent upon cytochrome P450 isoenzymes CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1 or CYP3A4. The terminal half-life of candesartan is approximately 9 hours. There is no accumulation following multiple doses.
Total plasma clearance of candesartan is about 0.37 ml/min/kg, with a renal clearance of about 0.19 ml/min/kg. The renal elimination of candesartan is both by glomerular filtration and active tubular secretion. Following an oral dose of ^{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 faeces as candesartan and 10% as the inactive metabolite.

Pharmacokinetics in special populations

In the elderly (over 65 years) C_{max} and AUC of candesartan are increased by approximately 50% and 80%, respectively in comparison to young subjects. However, the blood pressure response and the incidence of adverse events are similar after a given dose of candesartan cilexetil in young and elderly patients (see section 4.2).

In patients with mild to moderate renal impairment C_{max} and AUC of candesartan increased during repeated dosing by approximately 50% and 70%, respectively, but $t_{1/2}$ was not altered, compared to patients with normal renal function. The corresponding changes in patients with severe renal impairment were approximately 50% and 110%, respectively. The terminal $t_{1/2}$ of candesartan was approximately doubled in patients with severe renal impairment. The AUC of candesartan in patients undergoing haemodialysis was similar to that in patients with severe renal impairment.
In two studies, both including patients with mild to moderate hepatic impairment, there was an increase in the mean AUC of candesartan of approximately 20% in one study and 80% in the other study (see section 4.2). There is no experience in patients with severe hepatic impairment.

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, haemoglobin, haematocrit). Effects on the kidneys (such as interstitial nephritis, tubular distension, basophilic tubules; increased plasma concentrations of urea and creatinine) were induced by candesartan which could be secondary to the hypotensive effect leading to alterations of renal perfusion. Furthermore, candesartan induced hyperplasia/hypertrophy of the juxtaglomerular cells. These changes were considered to be caused by the pharmacological action of candesartan. For therapeutic doses of candesartan in humans, the hyperplasia/hypertrophy of the renal juxtaglomerular cells does not seem to have any relevance.
Fetotoxicity has been observed in late pregnancy (see section 4.6).
Data from *in vitro* and *in vivo* mutagenicity testing indicate that candesartan will not 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
Maize starch
Dibutyl sebacate
Sodium laurilsulfate
Hydroxypropylcellulose
Carmellose calcium
Magnesium stearate
Iron oxide red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

Blister PVC/PVDC/Aluminium
Pack sizes: 7, 10, 14, 28, 30, 50, 56, 60, 84, 90, 98, 100 tablets in a box.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Miklich Laboratorios S.L., Cuevas bajas, s/n - Of.23, Edificio Picasso, 29004 Malaga, Spain.

8 MARKETING AUTHORISATION NUMBER(S)

PL 35084/0003 & 7

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

12/03/2012

10 DATE OF REVISION OF THE TEXT

12/03/2012

1 NAME OF THE MEDICINAL PRODUCT

Candesartan cilexetil 16 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 16 mg candesartan cilexetil.
Excipient:

	16 mg tablets
Lactose monohydrate	82.020 mg

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.
16 mg: Round, slightly pink, biconvex, one side scored tablets.

The scoreline is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of essential hypertension in adults.
Treatment of adult patients with heart failure and impaired left ventricular systolic function (left ventricular ejection fraction ≤ 40%) as add-on therapy to Angiotensin Converting Enzyme (ACE) inhibitors or when ACE inhibitors are not tolerated (see section 5.1).

4.2 Posology and method of administration

Posology in hypertension
The recommended initial dose and usual maintenance dose of Candesartan cilexetil is 8 mg once daily. Most of the antihypertensive effect is attained within 4 weeks. In some patients whose blood pressure is not adequately controlled, the dose can be increased to 16 mg once daily and to a maximum of 32 mg once daily. Therapy should be adjusted according to blood pressure response.
Candesartan cilexetil may also be administered with other antihypertensive agents. Addition of hydrochlorothiazide has been shown to have an additive antihypertensive effect with various doses of Candesartan cilexetil.

Elderly population
No initial dosage adjustment is necessary in elderly patients.

Patients with intravascular volume depletion
An initial dose of 4 mg may be considered in patients at risk for hypotension, such as patients with possible volume depletion (see section 4.4).

Patients with renal impairment
The starting dose is 4 mg in patients with renal impairment, including patients on haemodialysis. The dose should be titrated according to response. There is limited experience in patients with very severe or end-stage renal impairment ($Cl_{creatinine}$ <15 ml/min) (see section 4.4).

Patients with hepatic impairment
An initial dose of 4 mg once daily is recommended in patients with mild to moderate hepatic impairment. The dose may be adjusted according to response. Candesartan cilexetil is contraindicated in patients with severe hepatic impairment and/or cholestasis (see sections 4.3 and 5.2).

Black patients
The antihypertensive effect of candesartan is less pronounced in black patients than in non-black patients. Consequently, uptitration of Candesartan cilexetil and concomitant therapy may be more frequently needed for blood pressure control in black than non-black patients (see section 5.1).

Posology in heart failure
The usual recommended initial dose of Candesartan cilexetil is 4 mg once daily. Up-titration to the target dose of 32 mg once daily (maximum dose) or the highest tolerated dose is done by doubling the dose at intervals of at least 2 weeks (see section 4.4). Evaluation of patients with heart failure should always comprise assessment of renal function including monitoring of serum creatinine and potassium. Candesartan cilexetil can be administered with other heart failure treatment, including ACE inhibitors,

beta-blockers, diuretics and digitalis or a combination of these medicinal products. The combination of an ACE inhibitor, a potassium-sparing diuretic (e.g. spironolactone) and Candesartan cilexetil is not recommended and should be considered only after careful evaluation of the potential benefits and risks (see sections 4.4, 4.8 and 5.1).

Special patient populations
No initial dose adjustment is necessary for elderly patients or in patients with intravascular volume depletion, renal impairment or mild to moderate hepatic impairment.

Paediatric population
The safety and efficacy of Candesartan cilexetil in children aged between birth and 18 years have not been established in the treatment of hypertension and heart failure. No data are available.

Method of administration
Oral use.
Candesartan cilexetil should be taken once daily with or without food.
The bioavailability of candesartan is not affected by food.

4.3 Contraindications
Hypersensitivity to the active substance or to any of the excipients.
Second and third trimester of pregnancy (see sections 4.4 and 4.6).
Severe hepatic impairment and/or cholestasis.

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 Candesartan cilexetil.
When Candesartan cilexetil is used in hypertensive patients with renal impairment, periodic monitoring of serum potassium and creatinine levels is recommended. There is limited experience in patients with very severe or end-stage renal impairment ($Cl_{creatinine}$ < 15 ml/min). In these patients Candesartan cilexetil should be carefully titrated with thorough monitoring of blood pressure.
Evaluation of patients with heart failure should include periodic assessments of renal function, especially in elderly patients 75 years or older, and patients with impaired renal function. During dose titration of Candesartan cilexetil, 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).

Concomitant therapy with an ACE inhibitor in heart failure
The risk of adverse reactions, especially renal function impairment and hyperkalaemia, may increase when candesartan is used in combination with an ACE inhibitor (see section 4.8). Patients with such treatment should be monitored regularly and carefully.

Haemodialysis
During dialysis the blood pressure may be particularly sensitive to AT_1-receptor blockade as a result of reduced plasma volume and activation of the renin-angiotensin-aldosterone system. Therefore Candesartan cilexetil should be carefully titrated with thorough monitoring of blood pressure in patients on haemodialysis.

Renal artery stenosis
Medicinal products that affect the renin-angiotensin-aldosterone system, including angiotensin II receptor antagonists (AIIRAs), may increase blood urea and serum creatinine in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney.

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

Hypotension
Hypotension may occur during treatment with Candesartan cilexetil in heart failure patients. It 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.

Anaesthesia and surgery
Hypotension may occur during anaesthesia and surgery in patients treated with angiotensin II antagonists due to blockade of the renin-angiotensin system. Very rarely, hypotension may be severe such that it may warrant the use of intravenous fluids and/or vasopressors.

Aortic and mitral valve stenosis (obstructive hypertrophic cardiomyopathy)
As with other vasodilators, special caution is indicated in patients suffering from haemodynamically relevant aortic or mitral valve stenosis, or obstructive hypertrophic cardiomyopathy.

Primary hyperaldosteronism
Patients with primary hyperaldosteronism will not generally respond to antihypertensive medicinal products acting through inhibition of the renin-angiotensin-aldosterone system. Therefore, the use of Candesartan cilexetil is not recommended.

Hyperkalaemia
Concomitant use of Candesartan cilexetil with potassium-sparing diuretics, potassium supplements, salt substitutes 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 treated with Candesartan cilexetil, hyperkalaemia may occur. Periodic monitoring of serum potassium is recommended. The combination of an ACE inhibitor, a potassium-sparing diuretic (e.g. spironolactone) and Candesartan cilexetil 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 ischaemic cardiopathy or ischaemic 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.

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 angiotensin II receptor antagonists should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

This medicinal product contains Lactose monohydrate.
Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction
Compounds which have been investigated in clinical pharmacokinetic studies include hydrochlorothiazide, warfarin, digoxin, oral contraceptives (i.e. ethinylestradiol/ levonorgestrel), glibenclamide, nifedipine and enalapril. No clinically significant pharmacokinetic interactions with these medicinal products have been identified.

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

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

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.

4.6 Fertility, pregnancy and lactation

Pregnancy

The use of AIIRAs is not recommended during the first trimester of pregnancy (see section 4.4).The use of AIIRAs is contraindicated during the second and third trimesters of pregnancy (see sections 4.3 and 4.4).

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Whilst there are no controlled epidemiological data on the risk with AIIRAs, similar risks may exist for this class of drug. Unless continued AIIRA therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with AIIRAs should be stopped immediately, and, if appropriate, alternative therapy should be started.

Exposure to AIIRA therapy during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia) (See section 5.3).
Should exposure to AIIRAs have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.
Infants whose mothers have taken AIIRAs should be closely observed for hypotension (see sections 4.3 and 4.4).

Lactation

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

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. However, it should be taken into account that occasionally dizziness or weariness may occur during treatment with Candesartan cilexetil.

4.8 Undesirable effects

Treatment of hypertension

In controlled clinical studies adverse reactions were mild and transient. The overall incidence of adverse events showed no association with dose or age. Withdrawals from treatment due to adverse events were similar with candesartan cilexetil (3.1%) and placebo (3.2%).

In a pooled analysis of clinical trial data of hypertensive patients, the following 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. By this definition, the most commonly reported adverse reactions were dizziness/vertigo, headache and respiratory infection.

The table below presents adverse reactions from clinical trials and post-marketing experience.

The frequencies used in the tables throughout 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)

System Organ Class	Frequency	Undesirable Effect
Infections and infestations	Common	Respiratory infection
Blood and lymphatic system disorders	Very rare	Leukopenia, neutropenia and agranulocytosis
Metabolism and nutrition disorders	Very rare	Hyperkalaemia, hyponatraemia
Nervous system disorders	Common	Dizziness/vertigo, headache
Gastrointestinal disorders	Very rare	Nausea
Hepato-biliary disorders	Very rare	Increased liver enzymes, abnormal hepatic function or hepatitis
Skin and subcutaneous tissue disorders	Very rare	Angioedema, rash, urticaria, pruritus
Musculoskeletal and connective tissue disorders	Very rare	Back pain, arthralgia, myalgia
Renal and urinary disorders	Very rare	Renal impairment, including renal failure in susceptible patients (see section 4.4)

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

Treatment of heart failure
The adverse experience 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 programme, comparing candesartan cilexetil in doses up to 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 hyperkalaemia, 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 table below presents adverse reactions from clinical trials and post-marketing experience.

System Organ Class	Frequency	Undesirable Effect
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
Gastrointestinal disorders	Very rare	Nausea
Hepato-biliary disorders	Very rare	Increased liver enzymes, abnormal hepatic function or hepatitis
Skin and subcutaneous tissue	Very rare	Angioedema, rash, urticaria, pruritus

disorders		
Musculoskeletal and connective tissue disorders	Very rare	Back pain, arthralgia, myalgia
Renal and urinary disorders	Common	Renal impairment, including renal failure in susceptible patients (see section 4.4)

Laboratory findings
Hyperkalaemia and renal impairment are common in patients treated with Candesartan cilexetil for the indication of heart failure. Periodic monitoring of serum creatinine and potassium is recommended (see section 4.4).

4.9 Overdose

Symptoms

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

Management

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Angiotensin II antagonists, plain, ATC code: C09CA06.

Angiotensin II is the primary vasoactive hormone of the renin-angiotensin-aldosterone system and plays a role in the pathophysiology of hypertension, heart failure and other cardiovascular disorders. It also has a role in the pathogenesis of end organ hypertrophy and damage. The major physiological effects of angiotensin II, such as vasoconstriction, aldosterone stimulation, regulation of salt and water homeostasis and stimulation of cell growth, are mediated via the type 1 (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, selective for AT_1 receptors, with tight binding to and slow dissociation from the receptor. It has no agonist activity.

Candesartan does not inhibit ACE, which converts angiotensin I to angiotensin II and degrades bradykinin. There is no effect on ACE and no potentiation of bradykinin or substance P. In controlled clinical trials comparing candesartan with ACE inhibitors, the incidence of cough was lower in patients receiving candesartan cilexetil. Candesartan does not bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation. The antagonism of the angiotensin II (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 indication of serious or exaggerated first dose hypotension or rebound effect after cessation of treatment.

After administration of a single dose of candesartan cilexetil, onset of antihypertensive effect generally occurs within 2 hours. With continuous treatment, most of the reduction in blood pressure with any dose is generally attained within four weeks and is sustained during long-term treatment. According to a meta-analysis, the average additional effect of a dose increase from 16 mg to 32 mg once daily was small. Taking into account the inter-individual variability, a more than average effect can be expected in some patients. Candesartan cilexetil once daily provides effective and smooth blood pressure reduction over 24 hours with little difference between maximum and trough effects during the dosing

interval. The antihypertensive effect and tolerability of candesartan and losartan were compared in two randomised, double-blind studies in a total of 1,268 patients with mild to moderate hypertension. The trough blood pressure reduction (systolic/diastolic) was 13.1/10.5 mmHg with candesartan cilexetil 32 mg once daily and 10.0/8.7 mmHg with losartan potassium 100 mg once daily (difference in blood pressure reduction 3.1/1.8 mmHg, $p<0.0001/p<0.0001$).

When candesartan cilexetil is used together with hydrochlorothiazide, the reduction in blood pressure is additive. An increased antihypertensive effect is also seen when candesartan cilexetil is combined with amlodipine or felodipine. Medicinal products that block the renin-angiotensin-aldosterone system have less pronounced antihypertensive effect in black patients (usually a low-renin population) than in non-black patients. This is also the case for candesartan. In an open-label clinical experience trial in 5,156 patients with diastolic hypertension, the blood pressure reduction during candesartan treatment was significantly less in black than non-black patients (14.4/10.3 mmHg vs 19.0/12.7 mmHg, $p<0.0001/p<0.0001$).

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

The effects of candesartan cilexetil 8-16 mg (mean dose 12 mg) once daily, on cardiovascular morbidity and mortality were evaluated in a randomised clinical trial with 4,937 elderly patients (aged 70-89 years; 21% aged 80 or above) with mild to moderate hypertension followed for a mean of 3.7 years (Study on Cognition and Prognosis in the Elderly). Patients received candesartan cilexetil or placebo with other antihypertensive treatment added as needed. The blood pressure was reduced from 166/90 to 145/80 mmHg in the candesartan group, and from 167/90 to 149/82mmHg 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).

Heart failure

Treatment with candesartan cilexetil reduces mortality, reduces hospitalisation 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) programme.
This placebo controlled, double-blind study programme in chronic heart failure (CHF) patients with NYHA functional class II to IV consisted of three separate studies: CHARM-Alternative (n=2,028) in patients with LVEF ≤ 40% not treated with an ACE inhibitor because of intolerance (mainly due to cough, 72%), CHARM-Added (n=2,548) in patients with LVEF ≤ 40% and treated with an ACE inhibitor, and CHARM-Preserved (n=3,023) in patients with LVEF > 40%. Patients on optimal CHF therapy at baseline were randomised to placebo or candesartan cilexetil (titrated from 4 mg or 8 mg once daily to 32 mg once daily or the highest tolerated dose, mean dose 24 mg) and followed for a median 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 CHARM-Alternative, the composite endpoint of cardiovascular mortality or first CHF hospitalisation was significantly reduced with candesartan in comparison with placebo (hazard ratio (HR) 0.77, 95% CI 0.67-0.89, $p<0.001$). This corresponds to a relative risk reduction of 23%. Of candesartan patients 33.0% (95%CI: 30.1 to 36.0) and of placebo patients 40.0% (95%CI: 37.0 to 43.1) experienced this endpoint, absolute difference 7.0% (95%CI: 11.2 to 2.8). Fourteen patients needed to be treated for the duration of the study to prevent one patient from dying of a cardiovascular event or being hospitalised for treatment of heart failure. The composite endpoint of all-cause mortality or first CHF hospitalisation was also significantly reduced with candesartan HR 0.80 (95% CI0.70-0.92, p=0.001). Of candesartan patients 36.6% (95%CI: 33.7 to 39.7) and of placebo patients 42.7% (95%CI: 39.6 to 45.8) experienced this endpoint, absolute difference 6.0% (95%CI: 10.3 to 1.8). Both the mortality and morbidity (CHF hospitalisation) components of these composite endpoints contributed to the favourable effects of candesartan. Treatment with candesartan cilexetil resulted in improved NYHA functional class (p=0.008).

In CHARM-Added, the composite endpoint of cardiovascular mortality or first CHF hospitalisation was significantly reduced with candesartan in comparison with placebo HR 0.85 (95%CI 0.75-0.96, p=0.011). This corresponds to a relative risk reduction of 15%. Of candesartan patients 37.9% (95%CI: 35.2 to 40.6) and of placebo patients 42.3% (95%CI: 39.6 to 45.1) experienced this endpoint, absolute difference 4.4% (95%CI: 8.2 to 0.6). Twenty-three patients needed to be treated for the duration of the study to prevent one patient from dying of a cardiovascular event or being hospitalised for treatment of heart failure. The composite endpoint of all-cause mortality or first CHF hospitalisation was also significantly reduced with candesartan HR 0.87 (95%CI 0.78-0.98, p=0.021). Of candesartan patients 42.2% (95%CI: 39.5 to 45.0) and of placebo patients 46.1% (95%CI: 43.4 to 48.9) experienced this endpoint, absolute difference 3.9% (95%CI: 7.8 to 0.1). Both the mortality and morbidity components of these composite endpoints contributed to the favourable effects of candesartan. Treatment with candesartan cilexetil resulted in improved NYHA functional class (p=0.020).

In CHARM-Preserved, no statistically significant reduction was achieved in the composite endpoint of cardiovascular mortality or first CHF hospitalisation, HR 0.89, 95%CI 0.77-1.03, 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, HR 0.88, (95% CI 0.79-0.98, p=0.018) and all three studies HR 0.91 (95%CI 0.83-1.00, p=0.055).

The beneficial effects of candesartan were consistent irrespective of age, gender and concomitant medication. Candesartan was effective also in patients taking both beta-blockers and ACE inhibitors at the same time, and the benefit was obtained whether or not patients were taking ACE inhibitors at the target dose recommended by treatment guidelines.
In patients with CHF and depressed left ventricular systolic function (left ventricular ejection fraction, LVEF $\leq$ 40%), candesartan decreases 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 and distribution

Following oral administration, candesartan cilexetil is converted to the active substance candesartan. The absolute bioavailability of candesartan is approximately 40% after an oral solution of candesartan cilexetil. The relative bioavailability of the tablet formulation compared with the same oral solution is approximately 34% with very little variability. The estimated absolute bioavailability of the tablet is therefore 14%. 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.
Candesartan is highly bound to plasma protein (more than 99%). The apparent volume of distribution of candesartan is 0.1 l/kg.
The bioavailability of candesartan is not affected by food.

Biotransformation and elimination

Candesartan is mainly eliminated unchanged via urine and bile and only to a minor extent eliminated by hepatic metabolism (CYP2C9). Available interaction studies indicate no effect on CYP2C9 and CYP3A4. Based on *in vitro* data, no interaction would be expected to occur *in vivo* with drugs whose metabolism is dependent upon cytochrome P450 isoenzymes CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1 or CYP3A4. The terminal half-life of candesartan is approximately 9 hours. There is no accumulation following multiple doses.
Total plasma clearance of candesartan is about 0.37 ml/min/kg, with a renal clearance of about 0.19 ml/min/kg. The renal elimination of candesartan is both by glomerular filtration and active tubular secretion. Following an oral dose of ^{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 faeces as candesartan and 10% as the inactive metabolite.

Pharmacokinetics in special populations

In the elderly (over 65 years) C_{max} and AUC of candesartan are increased by approximately 50% and 80%, respectively in comparison to young subjects. However, the blood pressure response and the incidence of adverse events are similar after a given dose of candesartan cilexetil in young and elderly patients (see section 4.2).

In patients with mild to moderate renal impairment C_{max} and AUC of candesartan increased during repeated dosing by approximately 50% and 70%, respectively, but $t_{1/2}$ was not altered, compared to patients with normal renal function. The corresponding changes in patients with severe renal impairment were approximately 50% and 110%, respectively. The terminal $t_{1/2}$ of candesartan was approximately doubled in patients with severe renal impairment. The AUC of candesartan in patients undergoing haemodialysis was similar to that in patients with severe renal impairment.
In two studies, both including patients with mild to moderate hepatic impairment, there was an increase in the mean AUC of candesartan of approximately 20% in one study and 80% in the other study (see section 4.2). There is no experience in patients with severe hepatic impairment.

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, haemoglobin, haematocrit). Effects on the kidneys (such as interstitial nephritis, tubular distension, basophilic tubules; increased plasma concentrations of urea and creatinine) were induced by candesartan which could be secondary to the hypotensive effect leading to alterations of renal perfusion. Furthermore, candesartan induced hyperplasia/hypertrophy of the juxtaglomerular cells. These changes were considered to be caused by the pharmacological action of candesartan. For therapeutic doses of candesartan in humans, the hyperplasia/hypertrophy of the renal juxtaglomerular cells does not seem to have any relevance.
Fetotoxicity has been observed in late pregnancy (see section 4.6).
Data from *in vitro* and *in vivo* mutagenicity testing indicate that candesartan will not 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
Maize starch
Dibutyl sebacate
Sodium laurilsulfate
Hydroxypropylcellulose
Carmellose calcium
Magnesium stearate
Iron oxide red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

Blister PVC/PVDC/Aluminium
Pack sizes: 7, 10, 14, 28, 30, 50, 56, 60, 84, 90, 98, 100 tablets in a box.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Miklich Laboratorios S.L., Cuevas bajas, s/n - Of.23, Edificio Picasso, 29004 Malaga, Spain.

8 MARKETING AUTHORISATION NUMBER(S)

PL 35084/0004 & 8

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
12/03/2012

10 DATE OF REVISION OF THE TEXT
12/03/2012

1 NAME OF THE MEDICINAL PRODUCT

Candesartan cilexetil 32 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 32 mg candesartan cilexetil.
Excipient:

	32 mg tablets
Lactose monohydrate	164.040 mg

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.
32 mg: Round, slightly pink, biconvex, one side scored tablets.

The scoreline is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of essential hypertension in adults.
Treatment of adult patients with heart failure and impaired left ventricular systolic function (left ventricular ejection fraction ≤ 40%) as add-on therapy to Angiotensin Converting Enzyme (ACE) inhibitors or when ACE inhibitors are not tolerated (see section 5.1).

4.2 Posology and method of administration

Posology in hypertension
The recommended initial dose and usual maintenance dose of Candesartan cilexetil is 8 mg once daily. Most of the antihypertensive effect is attained within 4 weeks. In some patients whose blood pressure is not adequately controlled, the dose can be increased to 16 mg once daily and to a maximum of 32 mg once daily. Therapy should be adjusted according to blood pressure response.
Candesartan cilexetil may also be administered with other antihypertensive agents. Addition of hydrochlorothiazide has been shown to have an additive antihypertensive effect with various doses of Candesartan cilexetil.

Elderly population
No initial dosage adjustment is necessary in elderly patients.

Patients with intravascular volume depletion
An initial dose of 4 mg may be considered in patients at risk for hypotension, such as patients with possible volume depletion (see section 4.4).

Patients with renal impairment
The starting dose is 4 mg in patients with renal impairment, including patients on haemodialysis. The dose should be titrated according to response. There is limited experience in patients with very severe or end-stage renal impairment ($Cl_{creatinine}$ <15 ml/min) (see section 4.4).

Patients with hepatic impairment
An initial dose of 4 mg once daily is recommended in patients with mild to moderate hepatic impairment. The dose may be adjusted according to response. Candesartan cilexetil is contraindicated in patients with severe hepatic impairment and/or cholestasis (see sections 4.3 and 5.2).

Black patients
The antihypertensive effect of candesartan is less pronounced in black patients than in non-black patients. Consequently, uptitration of Candesartan cilexetil and concomitant therapy may be more frequently needed for blood pressure control in black than non-black patients (see section 5.1).

Posology in heart failure
The usual recommended initial dose of Candesartan cilexetil is 4 mg once daily. Up-titration to the target dose of 32 mg once daily (maximum dose) or the highest tolerated dose is done by doubling the dose at intervals of at least 2 weeks (see section 4.4). Evaluation of patients with heart failure should always comprise assessment of renal function including monitoring of serum creatinine and potassium.
Candesartan cilexetil can be administered with other heart failure treatment, including ACE inhibitors,

beta-blockers, diuretics and digitalis or a combination of these medicinal products. The combination of an ACE inhibitor, a potassium-sparing diuretic (e.g. spironolactone) and Candesartan cilexetil is not recommended and should be considered only after careful evaluation of the potential benefits and risks (see sections 4.4, 4.8 and 5.1).

Special patient populations
No initial dose adjustment is necessary for elderly patients or in patients with intravascular volume depletion, renal impairment or mild to moderate hepatic impairment.

Paediatric population
The safety and efficacy of Candesartan cilexetil in children aged between birth and 18 years have not been established in the treatment of hypertension and heart failure. No data are available.

Method of administration
Oral use.
Candesartan cilexetil should be taken once daily with or without food.
The bioavailability of candesartan is not affected by food.

4.3 Contraindications
Hypersensitivity to the active substance or to any of the excipients.
Second and third trimester of pregnancy (see sections 4.4 and 4.6).
Severe hepatic impairment and/or cholestasis.

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 Candesartan cilexetil.
When Candesartan cilexetil is used in hypertensive patients with renal impairment, periodic monitoring of serum potassium and creatinine levels is recommended. There is limited experience in patients with very severe or end-stage renal impairment ($Cl_{creatinine}$ < 15 ml/min). In these patients Candesartan cilexetil should be carefully titrated with thorough monitoring of blood pressure.
Evaluation of patients with heart failure should include periodic assessments of renal function, especially in elderly patients 75 years or older, and patients with impaired renal function. During dose titration of Candesartan cilexetil, 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).

Concomitant therapy with an ACE inhibitor in heart failure
The risk of adverse reactions, especially renal function impairment and hyperkalaemia, may increase when candesartan is used in combination with an ACE inhibitor (see section 4.8). Patients with such treatment should be monitored regularly and carefully.

Haemodialysis
During dialysis the blood pressure may be particularly sensitive to AT_1-receptor blockade as a result of reduced plasma volume and activation of the renin-angiotensin-aldosterone system. Therefore Candesartan cilexetil should be carefully titrated with thorough monitoring of blood pressure in patients on haemodialysis.

Renal artery stenosis
Medicinal products that affect the renin-angiotensin-aldosterone system, including angiotensin II receptor antagonists (AIIRAs), may increase blood urea and serum creatinine in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney.

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

Hypotension
Hypotension may occur during treatment with Candesartan cilexetil in heart failure patients. It 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.

Anaesthesia and surgery
Hypotension may occur during anaesthesia and surgery in patients treated with angiotensin II antagonists due to blockade of the renin-angiotensin system. Very rarely, hypotension may be severe such that it may warrant the use of intravenous fluids and/or vasopressors.

Aortic and mitral valve stenosis (obstructive hypertrophic cardiomyopathy)
As with other vasodilators, special caution is indicated in patients suffering from haemodynamically relevant aortic or mitral valve stenosis, or obstructive hypertrophic cardiomyopathy.

Primary hyperaldosteronism
Patients with primary hyperaldosteronism will not generally respond to antihypertensive medicinal products acting through inhibition of the renin-angiotensin-aldosterone system. Therefore, the use of Candesartan cilexetil is not recommended.

Hyperkalaemia
Concomitant use of Candesartan cilexetil with potassium-sparing diuretics, potassium supplements, salt substitutes 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 treated with Candesartan cilexetil, hyperkalaemia may occur. Periodic monitoring of serum potassium is recommended. The combination of an ACE inhibitor, a potassium-sparing diuretic (e.g. spironolactone) and Candesartan cilexetil 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 ischaemic cardiopathy or ischaemic 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.

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 angiotensin II receptor antagonists should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

This medicinal product contains Lactose monohydrate.
Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction
Compounds which have been investigated in clinical pharmacokinetic studies include hydrochlorothiazide, warfarin, digoxin, oral contraceptives (i.e. ethinylestradiol/ levonorgestrel), glibenclamide, nifedipine and enalapril. No clinically significant pharmacokinetic interactions with these medicinal products have been identified.

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

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

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.

4.6 Fertility, pregnancy and lactation

Pregnancy

The use of AIIRAs is not recommended during the first trimester of pregnancy (see section 4.4).The use of AIIRAs is contraindicated during the second and third trimesters of pregnancy (see sections 4.3 and 4.4).

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Whilst there are no controlled epidemiological data on the risk with AIIRAs, similar risks may exist for this class of drug. Unless continued AIIRA therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with AIIRAs should be stopped immediately, and, if appropriate, alternative therapy should be started.

Exposure to AIIRA therapy during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia) (See section 5.3).
Should exposure to AIIRAs have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.
Infants whose mothers have taken AIIRAs should be closely observed for hypotension (see sections 4.3 and 4.4).

Lactation

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

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. However, it should be taken into account that occasionally dizziness or weariness may occur during treatment with Candesartan cilexetil.

4.8 Undesirable effects

Treatment of hypertension

In controlled clinical studies adverse reactions were mild and transient. The overall incidence of adverse events showed no association with dose or age. Withdrawals from treatment due to adverse events were similar with candesartan cilexetil (3.1%) and placebo (3.2%).

In a pooled analysis of clinical trial data of hypertensive patients, the following 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. By this definition, the most commonly reported adverse reactions were dizziness/vertigo, headache and respiratory infection.

The table below presents adverse reactions from clinical trials and post-marketing experience.

The frequencies used in the tables throughout 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)

System Organ Class	Frequency	Undesirable Effect
Infections and infestations	Common	Respiratory infection
Blood and lymphatic system disorders	Very rare	Leukopenia, neutropenia and agranulocytosis
Metabolism and nutrition disorders	Very rare	Hyperkalaemia, hyponatraemia
Nervous system disorders	Common	Dizziness/vertigo, headache
Gastrointestinal disorders	Very rare	Nausea
Hepato-biliary disorders	Very rare	Increased liver enzymes, abnormal hepatic function or hepatitis
Skin and subcutaneous tissue disorders	Very rare	Angioedema, rash, urticaria, pruritus
Musculoskeletal and connective tissue disorders	Very rare	Back pain, arthralgia, myalgia
Renal and urinary disorders	Very rare	Renal impairment, including renal failure in susceptible patients (see section 4.4)

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

Treatment of heart failure
The adverse experience 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 programme, comparing candesartan cilexetil in doses up to 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 hyperkalaemia, 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 table below presents adverse reactions from clinical trials and post-marketing experience.

System Organ Class	Frequency	Undesirable Effect
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
Gastrointestinal disorders	Very rare	Nausea
Hepato-biliary disorders	Very rare	Increased liver enzymes, abnormal hepatic function or hepatitis
Skin and subcutaneous tissue	Very rare	Angioedema, rash, urticaria, pruritus

disorders		
Musculoskeletal and connective tissue disorders	Very rare	Back pain, arthralgia, myalgia
Renal and urinary disorders	Common	Renal impairment, including renal failure in susceptible patients (see section 4.4)

Laboratory findings
Hyperkalaemia and renal impairment are common in patients treated with Candesartan cilexetil for the indication of heart failure. Periodic monitoring of serum creatinine and potassium is recommended (see section 4.4).

4.9 Overdose

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

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Angiotensin II antagonists, plain, ATC code: C09CA06.

Angiotensin II is the primary vasoactive hormone of the renin-angiotensin-aldosterone system and plays a role in the pathophysiology of hypertension, heart failure and other cardiovascular disorders. It also has a role in the pathogenesis of end organ hypertrophy and damage. The major physiological effects of angiotensin II, such as vasoconstriction, aldosterone stimulation, regulation of salt and water homeostasis and stimulation of cell growth, are mediated via the type 1 (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, selective for AT_1 receptors, with tight binding to and slow dissociation from the receptor. It has no agonist activity.

Candesartan does not inhibit ACE, which converts angiotensin I to angiotensin II and degrades bradykinin. There is no effect on ACE and no potentiation of bradykinin or substance P. In controlled clinical trials comparing candesartan with ACE inhibitors, the incidence of cough was lower in patients receiving candesartan cilexetil. Candesartan does not bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation. The antagonism of the angiotensin II (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 indication of serious or exaggerated first dose hypotension or rebound effect after cessation of treatment.

After administration of a single dose of candesartan cilexetil, onset of antihypertensive effect generally occurs within 2 hours. With continuous treatment, most of the reduction in blood pressure with any dose is generally attained within four weeks and is sustained during long-term treatment. According to a meta-analysis, the average additional effect of a dose increase from 16 mg to 32 mg once daily was small. Taking into account the inter-individual variability, a more than average effect can be expected in some patients. Candesartan cilexetil once daily provides effective and smooth blood pressure reduction over 24 hours with little difference between maximum and trough effects during the dosing

interval. The antihypertensive effect and tolerability of candesartan and losartan were compared in two randomised, double-blind studies in a total of 1,268 patients with mild to moderate hypertension. The trough blood pressure reduction (systolic/diastolic) was 13.1/10.5 mmHg with candesartan cilexetil 32 mg once daily and 10.0/8.7 mmHg with losartan potassium 100 mg once daily (difference in blood pressure reduction 3.1/1.8 mmHg, $p<0.0001/p<0.0001$).

When candesartan cilexetil is used together with hydrochlorothiazide, the reduction in blood pressure is additive. An increased antihypertensive effect is also seen when candesartan cilexetil is combined with amlodipine or felodipine. Medicinal products that block the renin-angiotensin-aldosterone system have less pronounced antihypertensive effect in black patients (usually a low-renin population) than in non-black patients. This is also the case for candesartan. In an open-label clinical experience trial in 5,156 patients with diastolic hypertension, the blood pressure reduction during candesartan treatment was significantly less in black than non-black patients (14.4/10.3 mmHg vs 19.0/12.7 mmHg, $p<0.0001/p<0.0001$).

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

The effects of candesartan cilexetil 8-16 mg (mean dose 12 mg) once daily, on cardiovascular morbidity and mortality were evaluated in a randomised clinical trial with 4,937 elderly patients (aged 70-89 years; 21% aged 80 or above) with mild to moderate hypertension followed for a mean of 3.7 years (Study on Cognition and Prognosis in the Elderly). Patients received candesartan cilexetil or placebo with other antihypertensive treatment added as needed. The blood pressure was reduced from 166/90 to 145/80 mmHg in the candesartan group, and from 167/90 to 149/82mmHg 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).

Heart failure

Treatment with candesartan cilexetil reduces mortality, reduces hospitalisation 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) programme.
This placebo controlled, double-blind study programme in chronic heart failure (CHF) patients with NYHA functional class II to IV consisted of three separate studies: CHARM-Alternative (n=2,028) in patients with LVEF $\leq$ 40% not treated with an ACE inhibitor because of intolerance (mainly due to cough, 72%), CHARM-Added (n=2,548) in patients with LVEF $\leq$ 40% and treated with an ACE inhibitor, and CHARM-Preserved (n=3,023) in patients with LVEF > 40%. Patients on optimal CHF therapy at baseline were randomised to placebo or candesartan cilexetil (titrated from 4 mg or 8 mg once daily to 32 mg once daily or the highest tolerated dose, mean dose 24 mg) and followed for a median 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 CHARM-Alternative, the composite endpoint of cardiovascular mortality or first CHF hospitalisation was significantly reduced with candesartan in comparison with placebo (hazard ratio (HR) 0.77, 95% CI 0.67-0.89, $p<0.001$). This corresponds to a relative risk reduction of 23%. Of candesartan patients 33.0% (95%CI: 30.1 to 36.0) and of placebo patients 40.0% (95%CI: 37.0 to 43.1) experienced this endpoint, absolute difference 7.0% (95%CI: 11.2 to 2.8). Fourteen patients needed to be treated for the duration of the study to prevent one patient from dying of a cardiovascular event or being hospitalised for treatment of heart failure. The composite endpoint of all-cause mortality or first CHF hospitalisation was also significantly reduced with candesartan HR 0.80 (95% CI0.70-0.92, p=0.001). Of candesartan patients 36.6% (95%CI: 33.7 to 39.7) and of placebo patients 42.7% (95%CI: 39.6 to 45.8) experienced this endpoint, absolute difference 6.0% (95%CI: 10.3 to 1.8). Both the mortality and morbidity (CHF hospitalisation) components of these composite endpoints contributed to the favourable effects of candesartan. Treatment with candesartan cilexetil resulted in improved NYHA functional class (p=0.008).

In CHARM-Added, the composite endpoint of cardiovascular mortality or first CHF hospitalisation was significantly reduced with candesartan in comparison with placebo HR 0.85 (95%CI 0.75-0.96, p=0.011). This corresponds to a relative risk reduction of 15%. Of candesartan patients 37.9% (95%CI: 35.2 to 40.6) and of placebo patients 42.3% (95%CI: 39.6 to 45.1) experienced this endpoint, absolute difference 4.4% (95%CI: 8.2 to 0.6). Twenty-three patients needed to be treated for the duration of the study to prevent one patient from dying of a cardiovascular event or being hospitalised for treatment of heart failure. The composite endpoint of all-cause mortality or first CHF hospitalisation was also significantly reduced with candesartan HR 0.87 (95%CI 0.78-0.98, p=0.021). Of candesartan patients 42.2% (95%CI: 39.5 to 45.0) and of placebo patients 46.1% (95%CI: 43.4 to 48.9) experienced this endpoint, absolute difference 3.9% (95%CI: 7.8 to 0.1). Both the mortality and morbidity components of these composite endpoints contributed to the favourable effects of candesartan. Treatment with candesartan cilexetil resulted in improved NYHA functional class (p=0.020).

In CHARM-Preserved, no statistically significant reduction was achieved in the composite endpoint of cardiovascular mortality or first CHF hospitalisation, HR 0.89, 95%CI 0.77-1.03, 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, HR 0.88, (95% CI 0.79-0.98, p=0.018) and all three studies HR 0.91 (95%CI 0.83-1.00, p=0.055).

The beneficial effects of candesartan were consistent irrespective of age, gender and concomitant medication. Candesartan was effective also in patients taking both beta-blockers and ACE inhibitors at the same time, and the benefit was obtained whether or not patients were taking ACE inhibitors at the target dose recommended by treatment guidelines.
In patients with CHF and depressed left ventricular systolic function (left ventricular ejection fraction, LVEF $\leq$ 40%), candesartan decreases 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 and distribution

Following oral administration, candesartan cilexetil is converted to the active substance candesartan. The absolute bioavailability of candesartan is approximately 40% after an oral solution of candesartan cilexetil. The relative bioavailability of the tablet formulation compared with the same oral solution is approximately 34% with very little variability. The estimated absolute bioavailability of the tablet is therefore 14%. 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.
Candesartan is highly bound to plasma protein (more than 99%). The apparent volume of distribution of candesartan is 0.1 l/kg.
The bioavailability of candesartan is not affected by food.

Biotransformation and elimination

Candesartan is mainly eliminated unchanged via urine and bile and only to a minor extent eliminated by hepatic metabolism (CYP2C9). Available interaction studies indicate no effect on CYP2C9 and CYP3A4. Based on *in vitro* data, no interaction would be expected to occur *in vivo* with drugs whose metabolism is dependent upon cytochrome P450 isoenzymes CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1 or CYP3A4. The terminal half-life of candesartan is approximately 9 hours. There is no accumulation following multiple doses.
Total plasma clearance of candesartan is about 0.37 ml/min/kg, with a renal clearance of about 0.19 ml/min/kg. The renal elimination of candesartan is both by glomerular filtration and active tubular secretion. Following an oral dose of ^{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 faeces as candesartan and 10% as the inactive metabolite.

Pharmacokinetics in special populations

In the elderly (over 65 years) C_{max} and AUC of candesartan are increased by approximately 50% and 80%, respectively in comparison to young subjects. However, the blood pressure response and the incidence of adverse events are similar after a given dose of candesartan cilexetil in young and elderly patients (see section 4.2).

In patients with mild to moderate renal impairment C_{max} and AUC of candesartan increased during repeated dosing by approximately 50% and 70%, respectively, but $t_{1/2}$ was not altered, compared to patients with normal renal function. The corresponding changes in patients with severe renal impairment were approximately 50% and 110%, respectively. The terminal $t_{1/2}$ of candesartan was approximately doubled in patients with severe renal impairment. The AUC of candesartan in patients undergoing haemodialysis was similar to that in patients with severe renal impairment.
In two studies, both including patients with mild to moderate hepatic impairment, there was an increase in the mean AUC of candesartan of approximately 20% in one study and 80% in the other study (see section 4.2). There is no experience in patients with severe hepatic impairment.

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, haemoglobin, haematocrit). Effects on the kidneys (such as interstitial nephritis, tubular distension, basophilic tubules; increased plasma concentrations of urea and creatinine) were induced by candesartan which could be secondary to the hypotensive effect leading to alterations of renal perfusion. Furthermore, candesartan induced hyperplasia/hypertrophy of the juxtaglomerular cells. These changes were considered to be caused by the pharmacological action of candesartan. For therapeutic doses of candesartan in humans, the hyperplasia/hypertrophy of the renal juxtaglomerular cells does not seem to have any relevance.
Fetotoxicity has been observed in late pregnancy (see section 4.6).
Data from *in vitro* and *in vivo* mutagenicity testing indicate that candesartan will not 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
Maize starch
Dibutyl sebacate
Sodium laurilsulfate
Hydroxypropylcellulose
Carmellose calcium
Magnesium stearate
Iron oxide red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

Blister PVC/PVDC/Aluminium
Pack sizes: 7, 10, 14, 28, 30, 50, 56, 60, 84, 90, 98, 100 tablets in a box.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Miklich Laboratorios S.L., Cuevas bajas, s/n - Of.23, Edificio Picasso, 29004 Malaga, Spain

8 MARKETING AUTHORISATION NUMBER(S)

PL 35084/0005 & 9

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
12/03/2012

10 DATE OF REVISION OF THE TEXT
12/03/2012

Module 3
Product Information Leaflets

Please note that the only mock-ups available are for licences PL 35084/0002-5. The marketing authorisation holder has stated that it does not intend to market the other licences at present and therefore, no UK-specific documents have been submitted. The marketing authorisation holder has committed to submit the UK PIL for the other licences to the regulatory authority for review before marketing them.

CONSILIENT HEALTH Ltd.

PACKAGE LEAFLET: INFORMATION FOR THE USER

Candesartan cilexetil 4 mg tablets
Candesartan cilexetil 8 mg tablets
Candesartan cilexetil 16 mg tablets
Candesartan cilexetil 32 mg tablets

Candesartan cilexetil

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

IN THIS LEAFLET:

1. WHAT CANDESARTAN CILEXETIL IS AND WHAT IT IS USED FOR

The name of your medicine is Candesartan cilexetil. The active ingredient is candesartan cilexetil. This belongs to a group of medicines called angiotensin II receptor antagonists. It works by making your blood vessels relax and widen. This helps to lower your blood pressure. It also makes it easier for your heart to pump blood to all parts of your body.

This is medicine is used for
- treating high blood pressure (hypertension) in adult patients.
- treating adult heart failure patients with reduced heart muscle function, in addition to Angiotensin Converting Enzyme (ACE) inhibitors or when ACE inhibitors cannot be used (ACE inhibitors are a group of medicines used to treat heart failure).

2. BEFORE YOU TAKE CANDESARTAN CILEXETIL

Do not take Candesartan cilexetil
- if you are allergic (hypersensitive) to candesartan cilexetil or any of the other ingredients of Candesartan cilexetil (see section 6).
- if you are more than 3 months pregnant. (It is also better to avoid Candesartan cilexetil in early pregnancy – see pregnancy section.)
- if you have severe liver disease or biliary obstruction (a problem with the drainage of the bile from the gall bladder).

If you are not sure if any of these apply to you, talk to your doctor or pharmacist before taking Candesartan cilexetil.

Take special care with Candesartan cilexetil
Before you take, or whilst you are taking Candesartan cilexetil, tell your doctor
- if you have heart, liver or kidney problems, or are on dialysis,
- if you have recently had a kidney transplant,
- if you are vomiting, have recently had severe vomiting, or have diarrhoea,
- if you have a disease of the adrenal gland called Conn's syndrome (also called primary hyperaldosteronism),
- if you have low blood pressure,
- if you have ever had a stroke,
- you must tell your doctor if you think that you are (or might become) pregnant. Candesartan cilexetil is not recommended in early pregnancy, and must not be taken if you are more than 3 months pregnant, as it may cause serious harm to your baby if used at that stage (see pregnancy section).

Your doctor may want to see you more often and do some tests if you have any of these conditions.

If you are going to have an operation, tell your doctor or dentist that you are taking Candesartan cilexetil. This is because Candesartan cilexetil, when combined with some anaesthetics, may cause a drop in blood pressure.

Use in children
There is no experience with the use of Candesartan cilexetil in children (below the age of 18 years). Therefore Candesartan cilexetil should not be given to children.

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.
Candesartan cilexetil can affect the way some other medicines work and some medicines can have an effect on Candesartan cilexetil. If you are using certain medicines, your doctor may need to do blood tests from time to time.

In particular, tell your doctor if you are using any of the following medicines:
- Other medicines to help lower your blood pressure, including beta-blockers, diazoxide and ACE inhibitors such as enalapril, captopril, lisinopril or ramipril.
- Non-steroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, naproxen or diclofenac, celecoxib or etoricoxib (medicines to relieve pain and inflammation).
- Acetylsalicylic acid (if you are taking more than 3 g each day) (medicine to relieve pain and inflammation).
- Potassium supplements or salt substitutes containing potassium (medicines that increase the amount of potassium in your blood).
- Heparin (a medicine for thinning the blood).
- Water tablets (diuretics).
- Lithium (a medicine for mental health problems).

Taking Candesartan cilexetil with food and drink
Candesartan cilexetil can be taken with or without food.
When you are prescribed Candesartan cilexetil, discuss with your doctor before drinking alcohol. Alcohol may make you feel faint or dizzy.

Pregnancy and breast-feeding
Ask your doctor or pharmacist for advice before taking any medicine.

Pregnancy
You must tell your doctor if you think you are (or might become) pregnant. Your doctor will normally advise you to stop taking Candesartan cilexetil before you become pregnant or as soon as you know you are pregnant and will advise you to take other medicines instead of Candesartan cilexetil. Candesartan cilexetil is not recommended in early pregnancy, and must not be taken when more than 3 months pregnant, as it may cause serious harm to your baby if used after the third month of pregnancy.

Breast-feeding
Tell your doctor if you are breast-feeding or about to start breast-feeding. Candesartan cilexetil is not recommended for mothers who are breast-feeding, and your doctor may choose another treatment for you if you wish to breast-feed, especially if your baby is newborn, or was born prematurely.

Driving and using machines
Some people may feel tired or dizzy when taking Candesartan cilexetil. If this happens to you, do not drive or use any tools or machines.

Important information about some of the ingredients of Candesartan cilexetil
Candesartan cilexetil contains lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this product.

3. HOW TO TAKE CANDESARTAN CILEXETIL

Always take Candesartan cilexetil exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure. It is important to keep taking Candesartan cilexetil every day.
You can take Candesartan cilexetil with or without food.
Swallow the tablet with a drink of water.
Try to take the tablet at the same time each day. This will help you to remember to take it.

High blood pressure
The usual dose of Candesartan cilexetil is 8 mg once a day. Your doctor may increase this dose to 16 mg once a day and further up to 32 mg once a day depending on blood pressure response.
In some patients, such as those with liver problems, kidney problems or those who recently have lost body fluids, e.g., through vomiting or diarrhoea or by using water tablets, the doctor may prescribe a lower starting dose.
Some black patients may have a reduced response to this type of medicine, when given as the only treatment, and these patients may need a higher dose.

Heart failure
The usual starting dose of Candesartan cilexetil is 4 mg once a day. Your doctor may increase your dose by doubling the dose at intervals of at least 2 weeks up to 32 mg once a day. Candesartan cilexetil can be taken together with other medicines for heart failure, and your doctor will decide which treatment is suitable for you.

If you take more Candesartan cilexetil than you should
If you take more Candesartan cilexetil than prescribed by your doctor, contact a doctor or a pharmacist immediately for advice.

If you forget to take Candesartan cilexetil
Do not take a double dose to make up for a forgotten tablet. Just take the next dose as normal.

If you stop taking Candesartan cilexetil
If you stop taking Candesartan cilexetil your blood pressure may increase again. Therefore do not stop taking Candesartan cilexetil without first talking to your doctor.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Candesartan cilexetil can cause side effects, although not everybody gets them. It is important that you are aware of what these side effects may be.

Stop taking Candesartan cilexetil and seek medical help immediately if you have any of the following allergic reactions:
- difficulties in breathing, with or without swelling of the face, lips, tongue and/or throat
- swelling of the face, lips, tongue and/or throat, which may cause difficulties in swallowing
- severe itching of the skin (with raised lumps)

Candesartan cilexetil may cause a reduction in number of white blood cells. Your resistance to infection may be decreased and you may notice tiredness, an infection or a fever. If this happens contact your doctor. Your doctor may occasionally do blood tests to check whether Candesartan cilexetil has had any effect on your blood (agranulocytosis).

Other possible side effects include:

Common *(affects 1 to 10 users in 100)*
- Feeling dizzy/spinning sensation.
- Headache.
- Respiratory infection.
- Low blood pressure. This may make you feel faint or dizzy.
- Changes in blood test results: an increased amount of potassium in your blood, especially if you already have kidney problems or heart failure. If this is severe you may notice tiredness, weakness, irregular heart beat or pins and needles.
- Effects on how your kidneys work, especially if you already have kidney problems or heart failure. In very rare cases, kidney failure may occur.

Very rare ***(affects less than 1 user in 10,000)***

- Swelling of the face, lips, tongue and/or throat.
- A reduction in your red or white blood cells. You may notice tiredness, an infection or a fever.
- Skin rash, lumpy rash (hives).
- Itching.
- Back pain, pain in joints and muscles.
- Changes in how your liver is working, including inflammation of the liver (hepatitis). You may notice tiredness, yellowing of your skin and the whites of your eyes and flu like symptoms.
- Nausea.
- Changes in blood test results: a reduced amount of sodium in your blood. If this is severe then you may notice weakness, lack of energy, or muscle cramps.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE CANDESARTAN CILEXETIL

Keep out of the reach and sight of children.

Do not use Candesartan cilexetil after the expiry date which is stated on the packaging.
The expiry date refers to the last day of that month.

Do not store above 30°C.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Candesartan cilexetil contains

- The active substance is candesartan cilexetil. Each tablet contains 4 mg, 8 mg, 16 mg or 32 mg candesartan cilexetil.
- The other ingredients are lactose monohydrate, maize starch, dibutyl sebacate, sodium laurilsulfate, hydroxypropylcellulose, carmellose calcium, magnesium stearate and iron oxide red (E172) – (8 mg, 16 mg and 32 mg tablets only)

What Candesartan cilexetil looks like and contents of the pack

4 mg tablets are round, white, biconvex, one side scored.
8 mg tablets are round, pinkish-white, biconvex, one side scored.
16 mg tablets are round, slightly pink, biconvex, one side scored.
32 mg tablets are round, slightly pink, biconvex, one side scored.

The scoreline is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

Boxes of 7, 10, 14, 28, 30, 50, 56, 60, 84, 90, 98, 100 tablets in blisters are available.
Not all pack sizes may be marketed.

Marketing Authorisation Holder:
Miklich Laboratorios S.L., Cuevas bajas, s/n - Of.23, Edificio Picasso, 29004 Malaga, Spain

Manufacturer:
1. Krka D.D., Šmarješka cesta 6, Novo mesto, SI-8501, Slovenia
2. TAD Pharma GmbH, Heinz-Lohmann-Straße 5, 27472 Cuxhaven, Germany

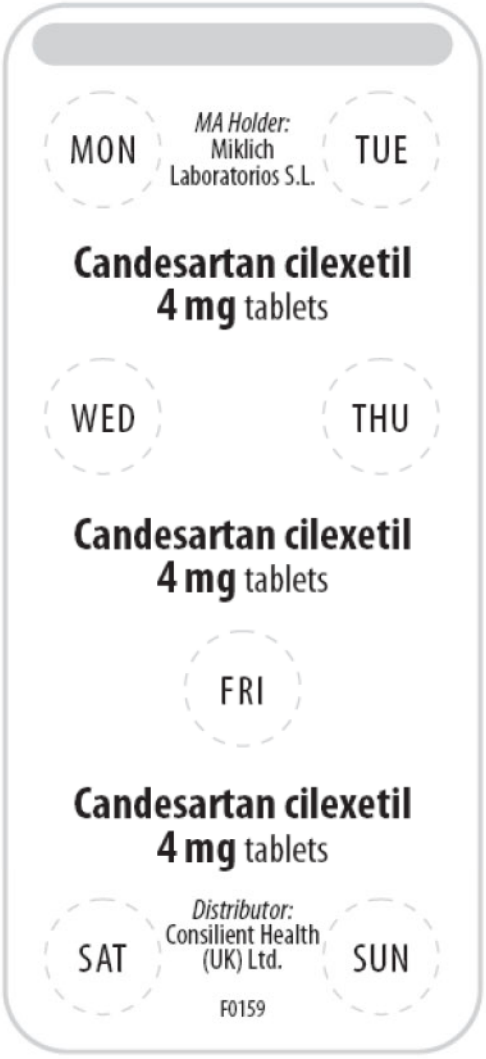
Distributed by: Consilient Health (UK) Ltd., 500 Chiswick High Road, London, W4 5RG.

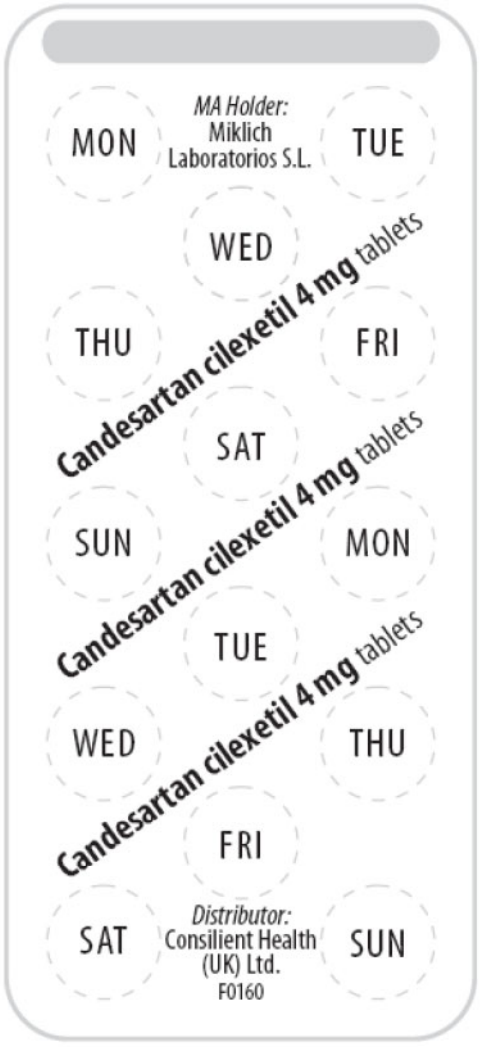
Date of leaflet revision: January 2012 P0147

Module 4
Labelling

Please note that the only mock-ups available are for licences PL 35084/0002-5, the 7 and 28 tablet pack size for the 4mg and the 28 tablet pack size for the 8mg, 16mg and 32mg strengths. The marketing authorisation holder has stated that it does not intend to market the other licences and pack sizes at present and therefore, no UK-specific documents have been submitted. The marketing authorisation holder has committed to submit the UK labelling for the other pack sizes licensed to the regulatory authority for review before marketing them.

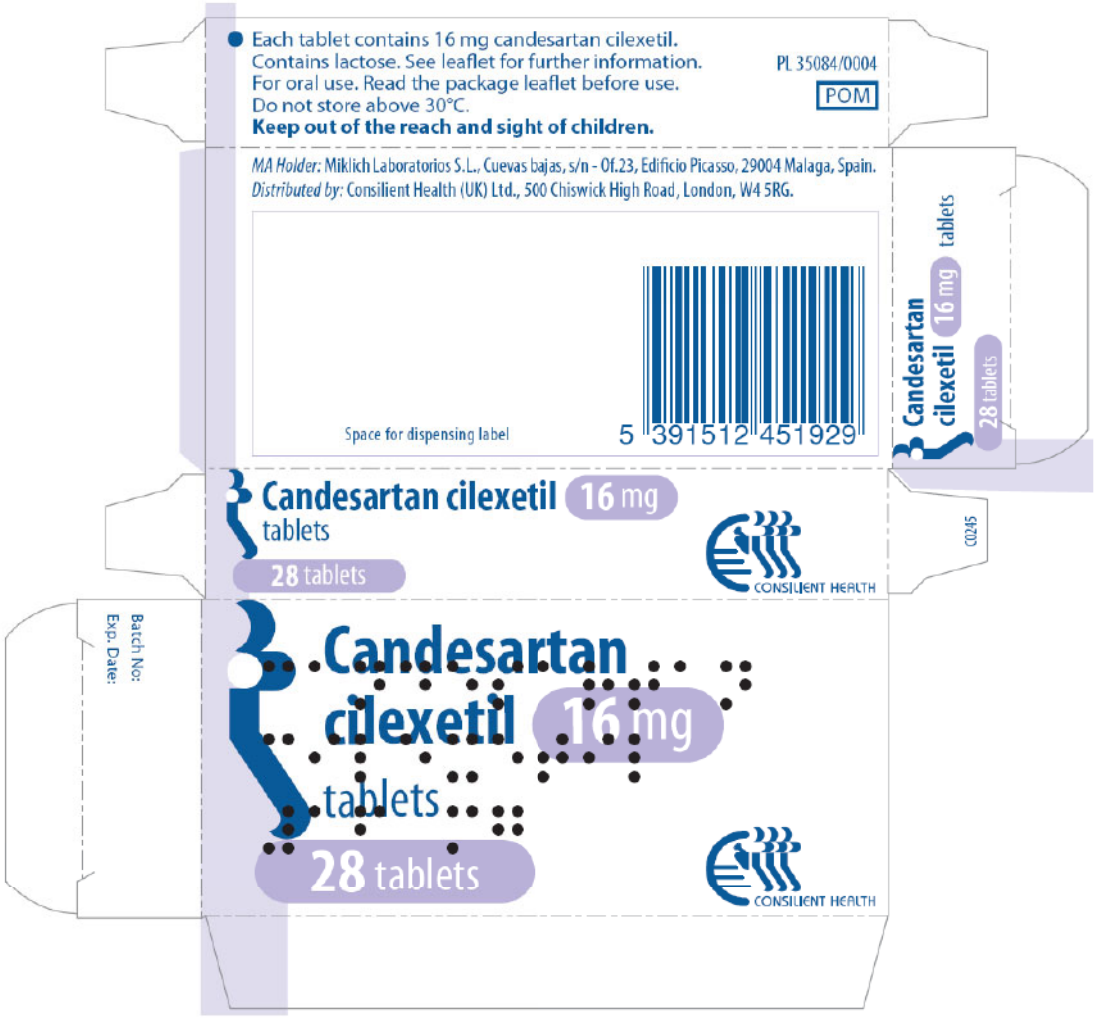

Each tablet contains 4 mg candesartan cilexetil.
Contains lactose. See leaflet for further information.
For oral use. Read the package leaflet before use.
Do not store above 30°C.
Keep out of the reach and sight of children.
PL 35084/0002
POM
MA Holder: Miklich Laboratorios S.L., Cuevas bajas, s/n - Of.23, Edificio Picasso, 29004 Malaga, Spain.
Distributed by: Consilient Health (UK) Ltd., 500 Chiswick High Road, London, W4 5RG.
Space for dispensing label
5 391512 451905
Candesartan cilexetil 4 mg tablets
28 tablets
CONSILIENT HEALTH
0243
Batch No:
Exp. Date:
Candesartan cilexetil 4 mg tablets
28 tablets
CONSILIENT HEALTH

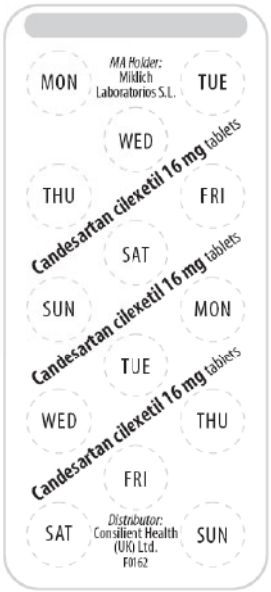

MON
MA Holder:
Miklich
Laboratorios S.L.
TUE
Candesartan cilexetil
4 mg tablets
WED
THU
Candesartan cilexetil
4 mg tablets
FRI
Candesartan cilexetil
4 mg tablets
SAT
Distributor:
Consilient Health
(UK) Ltd.
SUN
F0159

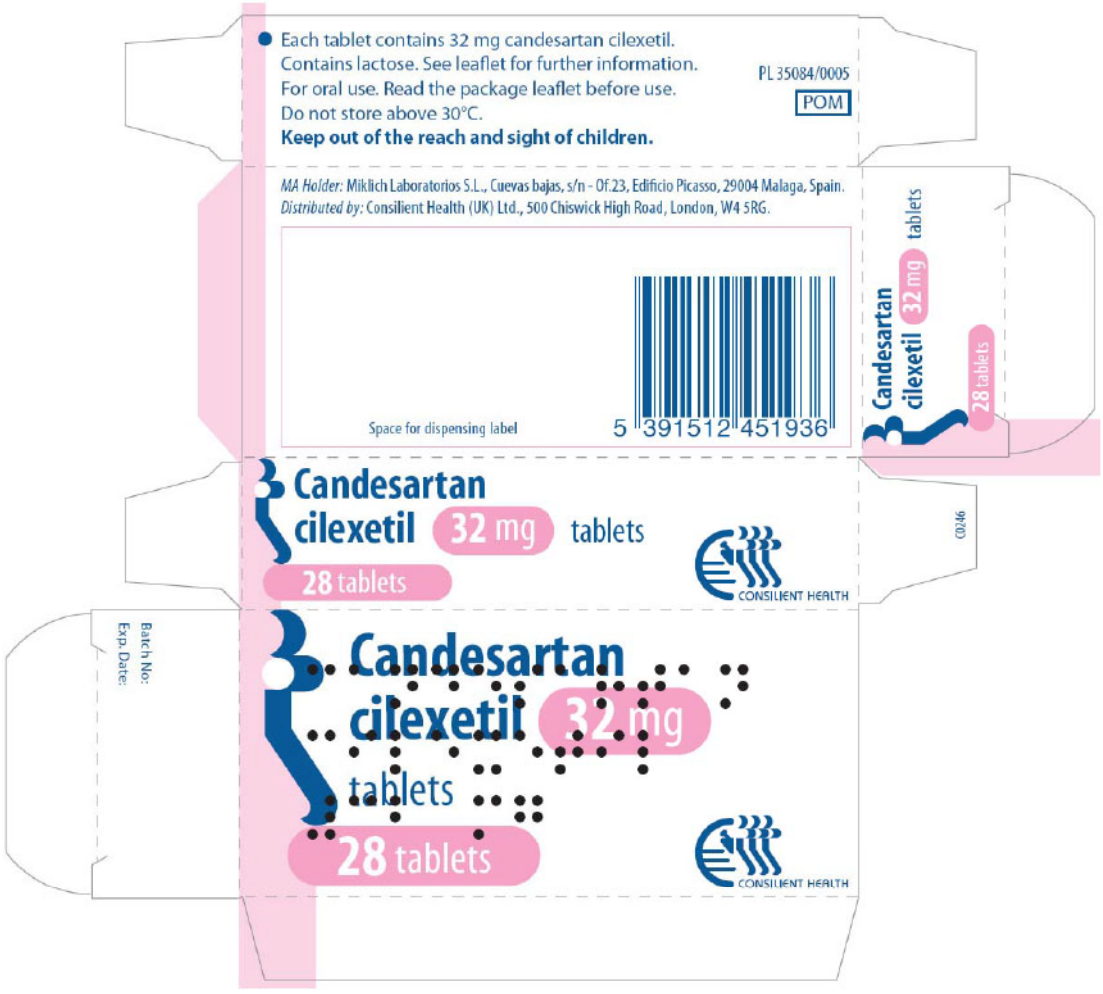

MON
MA Holder:
Miklich
Laboratorios S.L.
TUE
WED
THU
FRI
Candesartan cilexetil 4 mg tablets
SAT
SUN
MON
Candesartan cilexetil 4 mg tablets
TUE
WED
THU
Candesartan cilexetil 4 mg tablets
FRI
SAT
Distributor:
Consilient Health
(UK) Ltd.
SUN
F0160


Each tablet contains 8 mg candesartan cilexetil.
Contains lactose. See leaflet for further information.
For oral use. Read the package leaflet before use.
Do not store above 30°C.
Keep out of the reach and sight of children.
PL 35084/0003
POM
MA Holder: Miklich Laboratorios S.L., Cuevas bajas, s/n - Of.23, Edificio Picasso, 29004 Malaga, Spain.
Distributed by: Consilient Health (UK) Ltd., 500 Chiswick High Road, London, W4 5RG.
Space for dispensing label
5 391512 451912
Candesartan cilexetil 8 mg tablets
28 tablets
CONSILIENT HEALTH
0244
Batch No:
Exp. Date:
Candesartan cilexetil 8 mg
tablets
28 tablets
CONSILIENT HEALTH


MA Holder: Miklich Laboratorios S.L.
MON
TUE
WED
THU
FRI
SAT
SUN
Candesartan cilexetil 8 mg tablets
Candesartan cilexetil 8 mg tablets
Candesartan cilexetil 8 mg tablets
MON
TUE
WED
THU
FRI
SAT
SUN
Distributor: Consilient Health (UK) Ltd.
F0161


Each tablet contains 16 mg candesartan cilexetil.
Contains lactose. See leaflet for further information.
For oral use. Read the package leaflet before use.
Do not store above 30°C.
Keep out of the reach and sight of children.
PL 35084/0004
POM
MA Holder: Miklich Laboratorios S.L., Cuevas bajas, s/n - Of.23, Edificio Picasso, 29004 Malaga, Spain.
Distributed by: Consilient Health (UK) Ltd., 500 Chiswick High Road, London, W4 5RG.
Space for dispensing label
5 391512 451929
Candesartan cilexetil 16 mg tablets
28 tablets
CONSILIENT HEALTH
C0245
Batch No:
Exp. Date:
Candesartan cilexetil 16 mg tablets
28 tablets
CONSILIENT HEALTH


MA Holder: Miklich Laboratorios S.L.
MON
TUE
WED
THU
FRI
SAT
SUN
Candesartan cilexetil 16 mg tablets
Distributor: Consilient Health (UK) Ltd.
P0162


Each tablet contains 32 mg candesartan cilexetil.
Contains lactose. See leaflet for further information.
For oral use. Read the package leaflet before use.
Do not store above 30°C.
Keep out of the reach and sight of children.
PL 35084/0005
POM
MA Holder: Miklich Laboratorios S.L., Cuevas bajas, s/n - Of.23, Edificio Picasso, 29004 Malaga, Spain.
Distributed by: Consilient Health (UK) Ltd., 500 Chiswick High Road, London, W4 5RG.
Space for dispensing label
5 391512 451936
Candesartan cilexetil 32 mg tablets
28 tablets
CONSILIENT HEALTH
C0246
Batch No:
Exp Date:
Candesartan cilexetil 32 mg tablets
28 tablets
CONSILIENT HEALTH


MON
MA Holder: Miklich Laboratorios S.L.
TUE
WED
THU
FRI
SAT
SUN
MON
TUE
WED
THU
FRI
SAT
Distributor: Consilient Health (UK) Ltd.
F0163
SUN
Candesartan cilexetil 32 mg tablets
Candesartan cilexetil 32 mg tablets
Candesartan cilexetil 32 mg tablets

Module 5
Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, Austria, Belgium, Cyprus, Germany, Denmark, Greece, Spain, Finland, France, Hungary, Ireland, Italy, the Netherlands, Norway, Portugal, Sweden and the UK considered that the applications for Candesartan cilexetil 4 mg, 8 mg, 16 mg and 32 mg tablets could be approved.

Candesartan cilexetil 4 mg, 8 mg, 16 mg and 32 mg tablets are prescription only medicines (POM) and are indicated for the treatment of:

- Essential hypertension in adults.
- Adult patients with heart failure and impaired left ventricular systolic function (left ventricular ejection fraction ≤ 40%) as add-on therapy to Angiotensin Converting Enzyme (ACE) inhibitors or when ACE inhibitors are not tolerated.

These applications for Candesartan cilexetil 4 mg, 8 mg, 16 mg and 32 mg tablets were submitted according to Article 10.1 of Directive 2001/83/EC, as amended, claiming to be generic medicinal products of Blopress® tablets 4 mg, 8 mg, 16 mg and 32 mg, authorised in the UK to Takeda Europe Research and Development Centre GmbH on 29th April 1997 (PL 15661/0001-3 & 0040).

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 a specific angiotensin II receptor antagonist. It acts selectively on the AT1 receptor subtype, which is responsible for the known actions of angiotensin II. Candesartan is not known to bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation. Candesartan does not inhibit ACE (also known as kininase II) which converts angiotensin I to angiotensin II and degrades bradykinin.

No new non-clinical studies were conducted, which is acceptable given that the products contain a widely-used, well-known active substance. No clinical studies, with the exception of the bioequivalence studies, have been performed and none are required for these applications as the pharmacology of candesartan cilexetil is well-established.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the community, the RMS has accepted copies of current GMP Certificates or satisfactory inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	Candesartan cilexetil 4 mg Tablets Candesartan cilexetil 8 mg Tablets Candesartan cilexetil 16 mg Tablets Candesartan cilexetil 32 mg Tablets
Name(s) of the active substance(s) (INN)	Candesartan cilexetil
Pharmacotherapeutic classification (ATC code)	Angiotensin II antagonists, plain, (C09CA06)
Pharmaceutical form and strength(s)	4 mg Tablets 8 mg Tablets 16 mg Tablets 32 mg Tablets
Reference numbers for the Decentralised Procedure	UK/H/4347/001/DC UK/H/4347/002/DC UK/H/4347/003/DC UK/H/4347/004/DC UK/H/4626/001/DC UK/H/4626/002/DC UK/H/4626/003/DC UK/H/4626/004/DC
Reference Member State	United Kingdom (UK)
Member States concerned	UK/H/4347/001-4/DC: Austria (AT), Belgium (BE), Cyprus (CY), Germany (DE), Denmark (DK), Greece (EL), Spain (ES), Finland (FI), France (FR), Hungary (HU), Ireland (IE), Italy (IT), the Netherlands (NL), Norway (NO), Portugal (PT) and Sweden (SE) UK/H/4626/001-4/DC: Germany (DE), Spain (ES), France (FR), Italy (IT) and the Netherlands (NL)
Marketing Authorisation Number(s)	PL 35084/0002 PL 35084/0003 PL 35084/0004 PL 35084/0005 PL 35084/0006 PL 35084/0007 PL 35084/0008 PL 35084/0009
Name and address of the authorisation holder	Miklich Laboratorios S.L., Cuevas bajas, s/n - Of.23, Edificio Picasso, 29004 Malaga, Spain.

III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

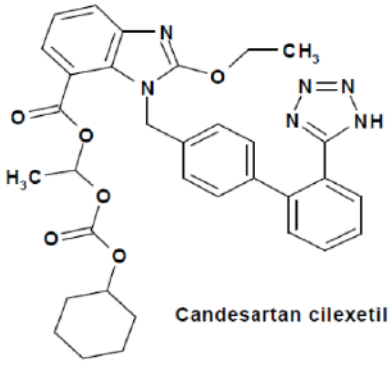
S. Active substance

INN/Ph.Eur name: Candesartan cilexetil

Chemical name:

- (±)-1-[[(cyclohexyloxy)carbonyl]oxy]ethyl-2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)[1,1'biphenyl]-4-yl]methyl]-1Hbenzimidazole-7-carboxylate

Structure:



Candesartan cilexetil

Physical form: A white to off-white powder.
Solubility: in soluble in water, soluble in methanol

Molecular formula: $C_{33}H_{34}N_6O_6$
Molecular weight: 610.66

Candesartan cilexetil complies with in-house specifications.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised. Satisfactory Certificates of Analysis have been provided for all working standards. Batch analysis data are provided and comply with the proposed specification.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines including the directive regarding contact with foodstuffs.

Stability studies have been performed with the active substance and no significant changes were observed. On the basis of the results, a suitable re-test period could be approved.

P. Medicinal Product

Other Ingredients

Other ingredients in the tablet consist of pharmaceutical excipients lactose monohydrate, maize starch, dibutyl sebacate, sodium laurilsulfate, hydroxypropylcellulose, carmellose calcium and magnesium stearate.
The 8 mg, 16 mg and 32 mg tablet strengths contain the additional excipient iron oxide red (E172).

With the exception of dibutyl sebacate, all excipients comply with their respective European Pharmacopoeia monographs. Dibutyl sebacate complies with the United States Pharmacopoeia (USP).

None of the excipients used contain material of human origin. The magnesium stearate contained in this product is sourced from vegetable origin and therefore no European Pharmacopoeia Certificate of Suitability for transmissible spongiform encephalopathies (TSE) is required.

The applicant has provided a declaration that the milk used in the production of the lactose monohydrate is sourced from healthy animals under the same conditions as those intended for human consumption.

No genetically modified organisms (GMO) have been used in the preparation of these products.

Pharmaceutical Development

The objective of the development programme was to produce safe, efficacious products containing candesartan cilexetil that could be considered generic medicinal products of Blopress® Tablets 4 mg, 8 mg, 16 mg and 32 mg.

The applicant has provided suitable product development sections. Valid justifications for the use and amounts of each excipient have been provided.

Comparative *in vitro* dissolution and impurity profiles have been provided for the proposed and reference products.

The reference products used in the bioequivalence studies are Blopress® 8 mg tabletten, licensed in Germany and Blopress® 32 mg tablets, licensed in Italy. These products are considered to be pharmaceutically equivalent to the UK reference products.

Manufacturing Process

A satisfactory batch formulae has been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results. Process validation data on pilot-scale batches of each strength have been provided and are satisfactory.
The applicant has committed to perform process validation on future commercial-scale batches.

Finished Product Specification

The finished product specifications are acceptable. Test methods have been described and adequately validated, as appropriate. Batch data have been provided and comply with the

release specifications. Certificates of Analysis have been provided for any working standards used.

Container-Closure System
These products are packaged in blisters composed of polyvinyl chloride (PVC), polyvinylidene chloride (PVdC) and aluminium. The blisters are then packaged into a box.

The pack sizes are 7, 10, 14, 28, 30, 50, 56, 60, 84, 90, 98, 100 tablets.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary product packaging complies with EU legislation.

Stability of the product
Stability studies were performed on batches of the finished products in the packaging proposed for marketing and in accordance with current guidelines. These data support a shelf-life of 2 years with the storage instructions 'Do not store above 30°C'. This is satisfactory.

Summary of Product Characteristics (SmPCs), Patient Information Leaflet (PIL) and Labelling
The SmPCs, PIL and labelling are pharmaceutically acceptable. The UK approved SmPCs, PIL and label mock-ups (PIL and label mock-ups available for PL 35084/0002-5 only) are included in modules 2, 3 and 4 of this report.

User testing results have been submitted for the PIL for this product. The results indicate that the PIL is in accordance with Article 59 of Council Directive 2001/83/EC, as amended and is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

MAA forms
The MAA forms are pharmaceutically satisfactory.

Quality Ovarall Summary
The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Conclusion
From a quality point of view, it is recommended that Marketing Authorisations are granted for these applications.

III.2 NON-CLINICAL ASPECTS

The pharmacodynamics, pharmacokinetics and toxicological properties of candesartan cilexetil are well-known. As candesartan cilexetil is a widely used, well-known active substance, the applicant has not provided any new non-clinical data and none are required. An overview based on literature is therefore appropriate.

Non-clinical Overview
The non-clinical overview has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

Environmental Risk Assessment
A satisfactory justification has been provided for the absence of an Environmental Risk Assessment (ERA).

Conclusion
From a non-clinical point of view, it is recommended that Marketing Authorisations are granted for these applications.

III.3 CLINICAL ASPECTS
Clinical Pharmacology

With the exception of the following bioequivalence studies, no new pharmacokinetic or pharmacodynamic data were submitted with these applications and none were required.

Pharmacokinetics

Bioequivalence study 1

A randomised, single-dose, 2-way, cross-over bioequivalence study to compare the pharmacokinetics of the test product Candesartan cilexetil 8 mg tablets versus the reference product Blopress® (candesartan cilexetil) Tablets 8 mg (Takeda Pharma GmbH, Germany) in healthy subjects under fasted conditions.

Blood samples were taken pre- and up to 36 hours post dose. There was a washout period of 7 days between each treatment period. Pharmacokinetic parameters were measured from the plasma and statistically analysed.

Results for candesartan cilexetil are presented below as log-transformed values for geometric means:

Candesartan cilexetil

Treatment	AUC_{0-t} (h.ng/mL)	$AUC_{0-\infty}$ (h.ng/mL)	C_{max} (ng/mL)
Test (T)	653.9	698.8	67.9
Reference (R)	633.7	691.9	59.7
T/R Ratio	103.19	101.00	113.65
(90% CI)	(97.85 – 108.82)	(96.31 – 105.91)	(104.40 – 123.71)

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration

The results for the primary variables indicated that the 90% confidence intervals test/reference ratio of geometric means for AUC_{0-t} and C_{max} for candesartan cilexetil lie within acceptable limits (80-125%). Thus, bioequivalence has been shown between the test and reference products in this study.

Bioequivalence study 2

A comparative, single-dose, 2-way, cross-over bioavailability study to compare the pharmacokinetics of the test product Candesartan cilexetil 32 mg tablets versus the reference product Blopress® (candesartan cilexetil) Tablets 32 mg (Takeda Italia Farmaceutici, Italy) in healthy subjects under fasted conditions.

Blood samples were taken pre- and up to 48 hours post dose. There was a washout period of 7 days between each treatment period. Pharmacokinetic parameters were measured from the plasma and statistically analysed.

Results for candesartan cilexetil are presented below as log-transformed values for geometric means:

Candesartan cilexetil

Treatment	AUC_{0-t} (h.ng/mL)	$AUC_{0-\infty}$ (h.ng/mL)	C_{max} (ng/mL)
Test (T3)	2139.91	2260.46	159.86
Reference (R)	2324.18	2532.32	157.48
T/R Ratio (90% CI)	92.07 (87.35 – 97.04)	89.26 (83.80 – 95.09)	101.51 (93.76 – 109.90)

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration

The results for the primary variables indicated that the 90% confidence intervals test/reference ratio of geometric means for AUC_{0-t} and C_{max} for candesartan cilexetil lie within acceptable limits (80-125%). Thus, bioequivalence has been shown between the test and reference products in this study.

As the product range meet all the criteria as specified in the Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1) for a biowaiver for the other strengths, the results and conclusions of the bioequivalence studies on the 8 mg and 32 mg strengths can be extrapolated to Candesartan cilexetil 4 mg and 16 mg tablets.

Efficacy
No new efficacy data were submitted with these generic applications and none were required.

Safety
With the exception of the data submitted during the bioequivalence studies, no new safety data were submitted with these generic applications and none were required. No new or unexpected safety concerns were raised during the bioequivalence studies.

Pharmacovigilance System
The RMS considers that the pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Risk Management Plan
A satisfactory justification has been provided for the absence of a Risk Management Plan.

Summary of Product Characteristics (SmPCs), Patient Information Leaflet (PIL) and Labelling
The SmPCs, PIL and labelling are clinically satisfactory and consistent with those for the reference products, where appropriate.

Clinical Overview
The clinical overview has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

MAA forms
The MAA forms are clinically satisfactory.

Conclusions
From a clinical point of view, it is recommended that Marketing Authorisations are granted for these applications.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY

The important quality characteristics of Candesartan cilexetil 4 mg, 8 mg, 16 mg and 32 mg tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit-risk balance.

NON-CLINICAL

No new non-clinical data were submitted and none are required for applications of this type.

CLINICAL

Bioequivalence has been demonstrated between the applicant's Candesartan cilexetil 8 mg and 32 mg tablets and the reference product Blopress® 8 mg and 32 mg tablets. These bioequivalence study results and conclusions can be extrapolated to Candesartan cilexetil 4 mg and 16 mg tablets.

No new or unexpected safety concerns arose from the bioequivalence studies.

The SmPCs, PIL and labelling are satisfactory and consistent with those for the reference products.

BENEFIT-RISK ASSESSMENT

The quality of the products is acceptable and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with candesartan cilexetil is considered to have demonstrated the therapeutic value of the compound. The benefit-risk ratio is, therefore, considered to be positive.

Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

Date submitted	Application type	Scope	Outcome