Public Assessment Report

Decentralised Procedure

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

(Candesartan cilexetil)

Procedure No: UK/H/3012/001-4/DC

UK Licence No: PL 18909/0355-8

ARROW GENERICS LIMITED
LAY SUMMARY

On 12 December 2011, Germany, Denmark, Finland, France, Poland, Spain, Sweden and the UK agreed to grant Marketing Authorisations to Arrow Generics Limited for the medicinal products Candesartan cilexetil 4 mg, 8 mg, 16 mg and 32 mg Tablets (PL 18909/0355-8; UK/H/3012/001-4/DC). The licences were granted via the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS). After a subsequent national phase, Marketing Authorisations were granted in the UK on 10 January 2012. These are Prescription-Only Medicines (POM).

Candesartan cilexetil belongs to a group of medicines called angiotensin II receptor antagonists. It works by making blood vessels relax and widen which helps to lower blood pressure. It also makes it easier for the heart to pump blood to all parts of the body.

This 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).

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 and Marketing Authorisations were granted.
# TABLE OF CONTENTS

Module 1: Information about initial procedure  Page 4

Module 2: Summary of Product Characteristics  Page 5

Module 3: Product Information Leaflet  Page 45

Module 4: Labelling  Page 47

Module 5: Scientific discussion during initial procedure  Page 52

- I Introduction
- II About the product
- III Scientific Overview and discussion
- III.1 Quality aspects
- III.2 Non-clinical aspects
- III.3 Clinical aspects
- IV Overall Conclusions and benefit-risk assessment

Module 6  Steps taken after initial procedure  Page 61
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, Article 10.1                  
| Active Substances            | Candesartan cilexetil                  
| Form                         | Tablets                                 
| Strength                     | 4 mg, 8 mg, 16 mg and 32 mg.            
| MA Holder                    | Arrow Generics Limited, Unit 2, Eastman Way, Stevenage Hertfordshire, SG1 4SZ, UK. 
| Reference Member State (RMS) | UK                                      
| Concerned Member State (CMS) | UK/H/001 and 004:Germany, Denmark, Finland, France, Spain and Sweden  
|                              | UK/H/002 and 003:Germany, Denmark, Finland, France, Poland, Spain and Sweden  
| Procedure Number             | UK/H/3012/001-4/DC                     
| Timetable                    | Day 192– 12 December 2011             

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.

Excipients:
95.1 mg lactose monohydrate/tablet.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Tablet.

Candesartan cilexetil 4 mg Tablets are white, round biconvex tablets, marked CC on one face and 04 on the other face and are scored on both faces.

The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Candesartan is indicated for the:

- Treatment of essential hypertension in adults.
- Treatment of adult patients with heart failure and impaired left ventricle systolic function (left ventricular ejection fraction $\leq 40\%$) 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 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 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.

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 ($\text{Cl}_{\text{creatinine}} \leq 15 \text{ ml/min}$). (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 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, up-titration of candesartan and concomitant therapy may be more frequently needed for blood pressure control in black patients than in non-black patients (see section 5.1).

**Posology in Heart Failure**

The usual recommended initial dose of Candesartan 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 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 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 in children aged between birth and 18 years has not been established in the treatment of hypertension and heart failure. No data are available.

**Method of administration**

Oral use.

Candesartan should be taken once daily with or without food. The bioavailability of candesartan is not affected by food.

### 4.3 Contraindications

- Hypersensitivity to candesartan cilexetil or to any of the excipients.
- Second and third trimesters 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.

When Candesartan 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 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, 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 AT1-receptor blockade as a result of reduced plasma volume and activation of the renin-angiotensin-aldosterone system. Therefore Candesartan 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 in patients with a recent kidney transplantation.

Hypotension
Hypotension may occur during treatment with candesartan 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 rennin-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 reninangiotensin-aldosterone system. Therefore, the use of candesartan is not recommended in this population.

Hyperkalaemia
Concomitant use of candesartan 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, 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 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.

These tablets contain lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

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

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 during breastfeeding, candesartan is not recommended and alternative treatments with better established safety profiles during breastfeeding 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 of candesartan 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.

4.8 Undesirable effects

Treatment of hypertension

In controlled clinical studies adverse events 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, 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.

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

Laboratory findings
In general, there were no clinically important influences of candesartan 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. 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 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 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.

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Frequency</th>
<th>Undesirable Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Very rare</td>
<td>Leukopenia, neutropenia and agranulocytosis</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Common</td>
<td>Hyperkalaemia</td>
</tr>
<tr>
<td></td>
<td>Very rare</td>
<td>Hyponatraemia</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Very rare</td>
<td>Dizziness, headache</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Common</td>
<td>Hypotension</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Very rare</td>
<td>Nausea</td>
</tr>
<tr>
<td>Hepato-biliary disorders</td>
<td>Very rare</td>
<td>Increased liver enzymes, abnormal hepatic function or hepatitis</td>
</tr>
<tr>
<td>System Organ Class</td>
<td>Frequency</td>
<td>Undesirable Effect</td>
</tr>
<tr>
<td>--------------------------------------------</td>
<td>------------</td>
<td>-----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Very rare</td>
<td>Angioedema, rash, urticaria, pruritus</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Very rare</td>
<td>Back pain, arthralgia, myalgia</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Common</td>
<td>Renal impairment, including renal failure in susceptible patients (see section 4.4)</td>
</tr>
</tbody>
</table>

**Laboratory findings**

Hyperkalaemia and renal impairment are common in patients treated with candesartan 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, supportive 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 C09C A06.

Angiotensin II is the primary vasoactive hormone of the renin-angiotensinaldosterone 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 149/82 mmHg in the control group. There was no statistically significant difference in the primary endpoint, major cardiovascular events (cardiovascular mortality, non-fatal stroke and non-fatal myocardial infarction). There were 26.7 events per 1000 patient-years in the candesartan group versus 30.0 events per 1000 patient-years in the control group (relative risk 0.89, 95% CI 0.75 to 1.06, p=0.19).

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 to 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% CI: 0.70 to 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 to 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 to 0.98, p=0.011). 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 to 1.03, p=0.118).

All-cause mortality was not statistically significant when examined separately in each of the three CHARM studies. However, all-cause mortality was also assessed in pooled populations, CHARM-Alternative and CHARM-Added HR 0.88 (95% CI: 0.79 to 0.98, p=0.018) and all three studies HR 0.91 (95% CI: 0.83 to 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 ≤ 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\text{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) $C_{\text{max}}$ and AUC of candesartan are increased by approximately 50% and 80%, respectively in comparison to young subjects. However, the blood pressure response and the incidence of adverse events are similar after a given dose of candesartan in young and elderly patients (see section 4.2).

In patients with mild to moderate renal impairment $C_{\text{max}}$ 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**

- Docusate sodium
- Sodium laurilsulphate
- Carmellose calcium
- Pregelatinised maize starch
- Hydroxypropylcellulose
- Lactose monohydrate
- Magnesium stearate (E572)

**6.2 Incompatibilities**

Not applicable.

**6.3 Shelf life**

2 years

**6.4 Special precautions for storage**

Do not store above 25°C.
6.5 Nature and contents of container
PVC/PE/PVDC aluminum blister with 7, 14, 28, 30, 50, 56, 70, 84, 90, 98, 100 and 250 (4/8/16mg only) tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORITY HOLDERS
Arrow Generics Limited
Unit 2, Eastman Way
Stevenage
Hertfordshire
SG1 4SZ
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 18909/0355

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
10/01/2012

10 DATE OF REVISION OF THE TEXT
10/01/2012
1 NAME OF THE MEDICINAL PRODUCT
Candesartan cilexetil 8 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 8 mg candesartan cilexetil.

Excipients:
190.1 mg lactose monohydrate/tablet.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Tablet.

Candesartan cilexetil 8 mg tablets are white, round biconvex tablets, marked CC on one face and 08 on the other face and are scored on both faces.

The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Candesartan is indicated for the:

- Treatment of essential hypertension in adults.
- Treatment of adult patients with heart failure and impaired left ventricle 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 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 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.

**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 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, up titration of candesartan and concomitant therapy may be more frequently needed for blood pressure control in black patients than in non-black patients (see section 5.1).
Posology in Heart Failure

The usual recommended initial dose of Candesartan 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 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 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 in children aged between birth and 18 years has not been established in the treatment of hypertension and heart failure. No data are available.

Method of administration

Oral use.

Candesartan should be taken once daily with or without food. The bioavailability of candesartan is not affected by food.

4.3 Contraindications

• Hypersensitivity to candesartan cilexetil or to any of the excipients.
• Second and third trimesters 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.

When Candesartan 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 (C\text{creatinine} < 15 \, \text{ml/min}). In these patients Candesartan 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, monitoring of serum creatinine and potassium is recommended. Clinical trials in heart failure did not include patients with serum creatinine >265 \, \mu\text{mol/L} (>3 \, \text{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\text{1}-receptor blockade as a result of reduced plasma volume and activation of the renin-angiotensin-aldosterone system. Therefore Candesartan 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 in patients with a recent kidney transplantation.

**Hypotension**

Hypotension may occur during treatment with candesartan 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 rennin-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 reninangiotensin-aldosterone system. Therefore, the use of candesartan is not recommended in this population.

**Hyperkalaemia**

Concomitant use of candesartan 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, 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 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.

These tablets contain lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

**Pregnancy**

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

**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. ethinylenestradiol/ 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 contra-indicated during the second and third trimesters of pregnancy (see section 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 drugs. Unless continued AIIRA therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with AIIRAs should be stopped immediately and, if appropriate, alternative therapy should be started.

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 during breastfeeding, candesartan is not recommended and alternative treatments with better established safety profiles during breastfeeding 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 of candesartan 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.

### 4.8 Undesirable effects

#### Treatment of hypertension

In controlled clinical studies adverse events 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, 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 section 4.8 are: very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000); very rare (< 1/10,000)

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

Laboratory findings

In general, there were no clinically important influences of candesartan 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. 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 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 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.
Hyperkalaemia and renal impairment are common in patients treated with candesartan 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, supportive 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 C09C A06.

Angiotensin II is the primary vasoactive hormone of the renin-angiotensinaldosterone 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 149/82 mmHg in the control group. There was no statistically significant difference in the primary endpoint, major cardiovascular events (cardiovascular mortality, non-fatal stroke and non-fatal myocardial infarction). There were 26.7 events per 1000 patient-years in the candesartan group versus 30.0 events per 1000 patient-years in the control group (relative risk 0.89, 95% CI 0.75 to 1.06, p=0.19).

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 to 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% CI: 0.70 to 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 to 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 to 0.98, \( p=0.011 \)). 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 to 1.03, \( p=0.118 \)).

All-cause mortality was not statistically significant when examined separately in each of the three CHARM studies. However, all-cause mortality was also assessed in pooled populations, CHARM-Alternative and CHARM-Added \( HR = 0.88 \) (95% CI: 0.79 to 0.98, \( p=0.018 \)) and all three studies \( HR = 0.91 \) (95% CI: 0.83 to 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 \( (C_{\text{max}}) \) 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) $C_{\text{max}}$ and AUC of candesartan are increased by approximately 50% and 80%, respectively in comparison to young subjects. However, the blood pressure response and the incidence of adverse events are similar after a given dose of candesartan in young and elderly patients (see section 4.2).

In patients with mild to moderate renal impairment $C_{\text{max}}$ 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

- Docusate sodium
- Sodium laurilsulphate
- Carmellose calcium
- Pregelatinised maize starch
- Hydroxypropylcellulose
- Lactose monohydrate
- Magnesium stearate (E572)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

PVC/PE/PVDC aluminum blister with 7, 14, 28, 30, 50, 56, 70, 84, 90, 98, 100 and 250 (4/8/16mg only) tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.
PAR Candesartan cilexetil 4 mg, 8 mg, 16 mg and 32 mg Tablets
UK/H/3012/001-4/DC

MARKETING AUTHORISATION HOLDER
Arrow Generics Limited
Unit 2, Eastman Way
Stevenage
Hertfordshire
SG1 4SZ
United Kingdom

MARKETING AUTHORISATION NUMBER(S)
PL 18909/0356

DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
10/01/2012

DATE OF REVISION OF THE TEXT
10/01/2012
1 NAME OF THE MEDICINAL PRODUCT
Candesartan cilexetil 16 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 16 mg candesartan cilexetil.

Excipients:
181.7 mg lactose monohydrate/tablet.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Tablet.

Candesartan cilexetil 16 mg Tablets are light red, round biconvex tablets, marked CC on one face and 16 on the other face and are scored on both faces.

The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Candesartan is indicated for the:

- Treatment of essential hypertension in adults.
- Treatment of adult patients with heart failure and impaired left ventricle 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 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 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.

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 (Clcreatinine <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 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 and concomitant therapy may be more frequently needed for blood pressure control in black patients than in non-black patients (see section 5.1).
Posology in Heart Failure

The usual recommended initial dose of Candesartan 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 can be administered with other heart failure treatment, including ACE inhibitors, beta-blockers, diuretics and digoxin or a combination of these medicinal products. The combination of an ACE inhibitor, a potassium-sparing diuretic (e.g. spironolactone) and candesartan 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 in children aged between birth and 18 years has not been established in the treatment of hypertension and heart failure. No data are available.

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

4.3 Contraindications
- Hypersensitivity to candesartan cilexetil or to any of the excipients.
- Second and third trimesters 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.

When Candesartan 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 (Cr\text{creatinine} < 15 ml/min). In these patients Candesartan 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, monitoring of serum creatinine and potassium is recommended. Clinical trials in heart failure did not include patients with serum creatinine >265 \(\mu\)mol/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 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 in patients with a recent kidney transplantation.

**Hypotension**
Hypotension may occur during treatment with candesartan 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 rennin-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 reninangiotensin-aldosterone system. Therefore, the use of candesartan is not recommended in this population.

**Hyperkalaemia**
Concomitant use of candesartan 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, 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 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.

These tablets contain lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

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

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 during breastfeeding, candesartan is not recommended and alternative treatments with better established safety profiles during breastfeeding 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 of candesartan 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.

4.8 Undesirable effects

Treatment of hypertension
In controlled clinical studies adverse events 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, 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 section 4.8 are: very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000); very rare (< 1/10,000)

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

**Laboratory findings**

In general, there were no clinically important influences of candesartan 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. 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 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 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.
<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Frequency</th>
<th>Undesirable Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Very rare</td>
<td>Angioedema, rash, urticaria, pruritus</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Very rare</td>
<td>Back pain, arthralgia, myalgia</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Common</td>
<td>Renal impairment, including renal failure in susceptible patients (see section 4.4)</td>
</tr>
</tbody>
</table>

**Laboratory findings**

Hyperkalaemia and renal impairment are common in patients treated with candesartan 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, supportive 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 C09C A06.

Angiotensin II is the primary vasoactive hormone of the renin-angiotensinaldosterone 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 149/82 mmHg in the control group. There was no statistically significant difference in the primary endpoint, major cardiovascular events (cardiovascular mortality, non-fatal stroke and non-fatal myocardial infarction). There were 26.7 events per 1000 patient-years in the candesartan group versus 30.0 events per 1000 patient-years in the control group (relative risk 0.89, 95% CI 0.75 to 1.06, p=0.19).

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 to 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% CI: 0.70 to 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 to 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 to 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 to 1.03, p=0.118).

All-cause mortality was not statistically significant when examined separately in each of the three CHARM studies. However, all-cause mortality was also assessed in pooled populations, CHARM-Alternative and CHARM-Added HR 0.88 (95% CI: 0.79 to 0.98, p=0.018) and all three studies HR 0.91 (95% CI: 0.83 to 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 ≤ 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 (Cmax) 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) $C_{\text{max}}$ and AUC of candesartan are increased by approximately 50% and 80%, respectively in comparison to young subjects. However, the blood pressure response and the incidence of adverse events are similar after a given dose of candesartan in young and elderly patients (see section 4.2).

In patients with mild to moderate renal impairment $C_{\text{max}}$ 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

- Docusate sodium
- Sodium laurilsulphate
- Carmellose calcium
- Pregelatinised maize starch
- Hydroxypropylcellulose
- Lactose monohydrate
- Magnesium stearate (E572)
- 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 30ºC.

6.5 Nature and contents of container

PVC/PE/PVDC aluminum blister with 7, 14, 28, 30, 50, 56, 70, 84, 90, 98, 100 and 250 (4/8/16mg only) tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Arrow Generics Limited
Unit 2, Eastman Way
Stevenage
Hertfordshire
SG1 4SZ
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 18909/0357

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
10/01/2012

10 DATE OF REVISION OF THE TEXT
10/01/2012
1 NAME OF THE MEDICINAL PRODUCT
Candesartan cilexetil 32 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 32 mg candesartan cilexetil.

Excipients:
363.5 mg lactose monohydrate/tablet.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Tablet.

Candesartan cilexetil 32 mg Tablets are light red, elliptic biconvex tablets, marked CC and 32 on the same face and are scored on both faces.

The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Candesartan is indicated for the:

- Treatment of essential hypertension in adults.
- Treatment of adult patients with heart failure and impaired left ventricle 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 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 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.

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 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, up titration of candesartan and concomitant therapy may be more frequently needed for blood pressure control in black patients than in non-black patients (see section 5.1).
Posology in Heart Failure

The usual recommended initial dose of Candesartan 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 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 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 in children aged between birth and 18 years has not been established in the treatment of hypertension and heart failure. No data are available.

Method of administration

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

4.3 Contraindications

- Hypersensitivity to candesartan cilexetil or to any of the excipients.
- Second and third trimesters 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.

When Candesartan 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 (Clcreatinine < 15 ml/min). In these patients Candesartan 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, 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 AT1-receptor blockade as a result of reduced plasma volume and activation of the renin-angiotensin-aldosterone system. Therefore Candesartan 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 in patients with a recent kidney transplantation.

**Hypotension**
Hypotension may occur during treatment with candesartan 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 rennin-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 reninangiotensin-aldosterone system. Therefore, the use of candesartan is not recommended in this population.

**Hyperkalaemia**
Concomitant use of candesartan 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, 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 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.

These tablets contain lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

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

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 during breastfeeding, candesartan is not recommended and alternative treatments with better established safety profiles during breastfeeding 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 of candesartan 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.

4.8 Undesirable effects

Treatment of hypertension

In controlled clinical studies adverse events 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, 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 section 4.8 are: very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000); very rare (< 1/10,000).

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

**Laboratory findings**

In general, there were no clinically important influences of candesartan 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. 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 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 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.
### Laboratory findings

Hyperkalaemia and renal impairment are common in patients treated with candesartan 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, supportive 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 C09C A06.

Angiotensin II is the primary vasoactive hormone of the renin-angiotensinaldosterone 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,
PAR Candesartan cilexetil 4 mg, 8 mg, 16 mg and 32 mg Tablets UK/H/3012/001-4/DC

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 to 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% CI: 0.70 to 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 to 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 to 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 to 1.03, p=0.118).

All-cause mortality was not statistically significant when examined separately in each of the three CHARM studies. However, all-cause mortality was also assessed in pooled populations, CHARM-Alternative and CHARM-Added HR 0.88 (95% CI: 0.79 to 0.98, p=0.018) and all three studies HR 0.91 (95% CI: 0.83 to 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 ≤ 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 \(C_{\text{max}}\) 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) $C_{\text{max}}$ and AUC of candesartan are increased by approximately 50% and 80%, respectively in comparison to young subjects. However, the blood pressure response and the incidence of adverse events are similar after a given dose of candesartan in young and elderly patients (see section 4.2).

In patients with mild to moderate renal impairment $C_{\text{max}}$ 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
Docusate sodium
Sodium laurilsulphate
Carmellose calcium
Pregelatinised maize starch
Hydroxypropylcellulose
Lactose monohydrate
Magnesium stearate (E572)
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
PVC/PE/PVDC aluminium blister with 7, 14, 28, 30, 50, 56, 70, 84, 90, 98, 100 and 250 (4/8/16mg only) tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORIZATION HOLDER
Arrow Generics Limited
Unit 2, Eastman Way
Stevenage
Hertfordshire
SG1 4SZ
United Kingdom

8 MARKETING AUTHORIZATION NUMBER(S)
PL 18909/0358

9 DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION
10/01/2012

10 DATE OF REVISION OF THE TEXT
10/01/2012
Module 3

PACKAGE LEAFLET: INFORMATION FOR THE USER
Candesartan cilexetil 4mg, 8mg, 16mg and 32mg Tablets

(Candesartan cilexetil)

Read all of this leaflet carefully before taking this medicine.
• Keep this leaflet. You may need to read it again.
• If you have any further questions, ask your doctor or your pharmacist.
• This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even in their use is the same as yours.
• If any of the side effects get 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 Tablets are and what they are used for
2. Before you take Candesartan cilexetil Tablets
3. How to take Candesartan cilexetil Tablets
4. Possible side effects
5. How to store Candesartan cilexetil Tablets
6. Further information

1. WHAT CANDESARTAN CILEXETIL TABLETS ARE AND WHAT THEY ARE USED FOR

The name of your medicine is Candesartan cilexetil Tablets. 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 medicine is used for:
• treating high blood pressure (hypertension) in adults.
• treating 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 Tablets

Do not take Candesartan cilexetil Tablets
• If you are allergic / hypersensitive to candesartan cilexetil or any of the other ingredients of Candesartan cilexetil Tablets (see section 3). If you are not sure if you are allergic / hypersensitive to it, speak to your doctor or pharmacist before taking Candesartan cilexetil Tablets.

Take special care with Candesartan cilexetil Tablets
Before you take, or whilst you are taking Candesartan cilexetil Tablets, tell your doctor:
• If you have heart, liver, or kidney problems, or you 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 Cushing’s syndrome (also called primary hyperaldosteronism).
• If you have low blood pressure.
• If you have ever had a stroke.
• If you must tell your doctor if you think you are (or might become) pregnant. Candesartan cilexetil Tablets are not recommended for 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 Tablets. This is because Candesartan cilexetil Tablets, 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 Tablets in children (below the age of 16 years). Therefore Candesartan cilexetil Tablets should not be given to children.

Using other medicines
Please tell your doctor or pharmacist if you are using, or have recently used any other medicines, including medicines obtained without a prescription.

Candesartan cilexetil Tablets can affect the way some other medicines work and some medicines can have an effect on Candesartan cilexetil Tablets. 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 lower your blood pressure, including beta-blockers, diuretics and ACE inhibitors such as enalapril, captopril, losartan or metolazone.
• Non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, naproxen, 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 Tablets with food and drink (in particular alcohol)
• You can take Candesartan cilexetil Tablets with or without food.
• When you are prescribed Candesartan cilexetil Tablets, discuss with your doctor before drinking alcohol. Alcohol may make you feel faint or dizzy.

Pregnancy and breast-feeding
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 Tablets before you become pregnant or as soon as you know you are pregnant and will advise you to take another medicine instead of Candesartan cilexetil Tablets. Candesartan cilexetil Tablets are 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 Tablets are 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 faint or dizzy when taking Candesartan cilexetil Tablets. If this happens to you, do not drive or use any tools or machines.

Important information about some of the ingredients of the Candesartan cilexetil Tablets
Candesartan cilexetil Tablets contain lactose which is a type of sugar. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. HOW TO TAKE Candesartan cilexetil TABLETS

Always take Candesartan cilexetil Tablets 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 Tablets every day.

You can take Candesartan cilexetil Tablets 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.
PAR Candesartan cilexetil 4 mg, 8 mg, 16 mg and 32 mg Tablets

UK/H/3012/001-4/DC

4. POSSIBLE SIDE EFFECTS

Like all medicines, Candesartan cilexetil Tablets 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 Tablets and seek medical help immediately if you have any of the following allergic reactions:

- difficulty 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 (including raised lumps)

Candesartan cilexetil Tablets may cause a reduction in the 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 Tablets has had any effect on your blood (granulocytes).

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 fits 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, infection or a fever.
- Skin rash, itchy 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.
- Neurone.

If any of the side effects get 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 Tablets

Keep out of the reach of children.

Do not use Candesartan cilexetil Tablets after the expiry date which is stated on the carton and blister after (EXP). The expiry date refers to the last day of that month.

Candesartan cilexetil 4 mg and 8 mg Tablets:
- Do not store above 25°C
- Candesartan cilexetil 16 mg and 32 mg Tablets:
- 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 Tablets contain

The active substance in Candesartan cilexetil Tablets is Candesartan. Each Candesartan cilexetil 4 mg Tablet contains 4 mg of Candesartan cilexetil. Each Candesartan cilexetil 8 mg Tablet contains 8 mg of Candesartan cilexetil. Each Candesartan cilexetil 16 mg Tablet contains 16 mg of Candesartan cilexetil. Each Candesartan cilexetil 32 mg Tablet contains 32 mg of Candesartan cilexetil. The other ingredients are: docusate sodium, sodium lauryl sulphate, carmellose sodium, pregelatinised maize starch, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate (E477) and iron oxide red (E172) (16 mg and 32 mg tablets only).

What Candesartan cilexetil Tablets look like and contents of the pack

Candesartan cilexetil Tablets are supplied in the following pack sizes:
- Blister packs with 7, 14, 28, 30, 56, 70, 84, 90, 98, 100 and 259 white, round biconvex tablets, marked CD on one face and 04 on the other face and scored on both faces.
- Candesartan cilexetil 8 mg Tablets are supplied in the following pack sizes:
- Blister packs with 7, 14, 28, 30, 56, 70, 84, 90, 98, 100 and 259 white, round biconvex tablets, marked CC on one face and 09 on the other face and scored on both faces.
- Candesartan cilexetil 16 mg Tablets are supplied in the following pack sizes:
- Blister packs with 7, 14, 28, 30, 56, 70, 84, 90, 98, 100 and 259 light red, round biconvex tablets, marked CC on one face and 09 on the other face and scored on both faces.
- Candesartan cilexetil 32 mg Tablets are supplied in the following pack sizes:
- Blister packs with 7, 14, 28, 30, 56, 70, 84, 90, 98, 100 and 259 light red, ollipic biconvex tablets, marked CC and 32 on the same face and are scored on both faces. Not all pack sizes may be marketed.

Marketing Authorisation Holder

Arrow Generics Limited, Unit 2, Eastman Way, Stevenage, Hertfordshire, SG1 4SZ, United Kingdom

Manufacturer

Genzyme-BHS Ltd., Vasal u. 13, 2048 Budapest, Hungary

This leaflet was last approved in 01/2012
Module 4
Labelling

Carton:
Blister:

Candesartan Cilexetil 4mg Tablets
(Candesartan cilexetil) Arrow Generics Limited

Candesartan Cilexetil 4mg Tablets
(Candesartan cilexetil) Arrow Generics Limited
Module 5
Scientific discussion during initial procedure

I  INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Member States considered that the applications for Candesartan cilexetil 4 mg, 8 mg, 16 mg and 32 mg Tablets (PL 18909/0355-8; UK/H/3012/001-4/DC) could be approved. These applications were submitted via the decentralised procedure, with the UK as Reference Member State (RMS) and Germany, Denmark, Finland, France, Poland, Spain and Sweden as Concerned Member State (CMS). These products are prescription-only medicines (POM).

Candesartan cilexetil 4 mg, 8 mg, 16 mg and 32 mg Tablets are indicated for the:

- treatment of essential hypertension in adults.
- treatment of adult patients with heart failure and impaired left ventricle 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 of SmPC).

These are abridged applications submitted under Article 10(1) of Directive 2001/83/EC as amended, cross-referring to Atacand 4 mg, 8 mg, 16 mg and 32 mg tablets (AstraZeneca A/S), which have been authorised in the EEA since 1997. The corresponding reference products in the UK are Amias 4 mg, 8 mg, 16 mg and 32 mg Tablets (Takeda UK Limited). The products used in the bioequivalence studies were Atacand 8 mg and 32 mg tablets, taken from the French market. It has been confirmed that these can be considered equivalent to the same products from the UK market.

Candesartan cilexetil is a pro-drug of candesartan. It is a highly selective antagonist of the angiotensin II subtype 1 receptor. Clinical effects mediated by the AT\textsubscript{1} receptors include vasoconstriction, increases in sodium retention, stimulation of aldosterone production and release, suppression of renin release, and activation of sympathetic activity. Inhibition of this system leads to a fall in blood pressure and can also reverse the pathological structural remodelling of the heart and vasculature. In addition, there is evidence that angiotensin II receptor antagonists may be renoprotective which is particularly valuable in patients with hypertension, diabetes and impaired renal function.

No new non-clinical studies were conducted, which is acceptable given that the products are intended to be generic versions of the originator products that have been licensed for over 10 years.

Two bioequivalence studies (single dose) were submitted to support these applications, comparing the test products Candesartan cilexetil 8 mg, and 32 mg Tablets (Arrow Generics Limited) with the reference products Atacand 8 mg and 32 mg tablets (AstraZeneca, France).

With the exception of the bioequivalence studies, no new clinical studies were conducted, which is acceptable given that the applications were for products that are intended to be generic versions of the originator products that have been licensed for over 10 years. The bioequivalence studies were carried out in accordance with Good Clinical Practice (GCP).
The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these product types at all sites responsible for the manufacture, assembly and batch release of these products.

The RMS and CMS considered that the applications could be approved with the end of procedure (Day 192) on 12 December 2011. After a subsequent national phase, the licences were granted in the UK on 10 January 2012.
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 |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Name(s) of the active substance(s) (INN)</td>
<td>Candesartan cilexetil</td>
</tr>
<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Angiotensin II antagonists, plain (C09C A06)</td>
</tr>
<tr>
<td>Pharmaceutical form and strength(s)</td>
<td>4 mg, 8 mg, 16 mg and 32 mg tablets</td>
</tr>
<tr>
<td>Reference numbers for the Mutual Recognition Procedure</td>
<td>UK/H/3012/001-4/DC</td>
</tr>
<tr>
<td>Reference Member State</td>
<td>United Kingdom</td>
</tr>
</tbody>
</table>
| Concerned Member State                          | UK/H/001 and 004:Germany, Denmark, Finland, France, Spain and Sweden           
UK/H/002 and 003:Germany, Denmark, Finland, France, Poland, Spain and Sweden |
| Marketing Authorisation Number(s)               | PL 18909/0355-8                                                                |
| Name and address of the authorisation holder     | Arrow Generics Limited, Unit 2, Eastman Way, Stevenage, Hertfordshire, SG1 4SZ, UK. |
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

S. Active substance

INN: Candesartan cilexetil
Chemical name: 2-Ethoxy-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-benzimidazole-7-carboxylic acid-1-[[Cyclohexyloxy]carbonyloxy]ethyl ester

2-ethoxy-1-[4-[(1H-tetrazol-5-yl)phenyl]benzyl]-7-benzimidazolecarboxylic acid-1-[[Cyclohexyloxy]carbonyloxy]ethyl ester

Structure:

![Structure diagram]

Molecular formula: \( C_{33}H_{34}N_6O_6 \)
Molecular mass: 610.66
Appearance: Candesartan cilexetil is a white or almost white crystalline powder. It is freely soluble in chloroform and tetrahydrofuran, soluble in acetone, sparingly soluble in ethanol, slightly soluble in methanol and acetonitrile and practically insoluble in water.

Candesartan cilexetil is not the subject of a European Pharmacopoeia monograph.

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 concerning contact with food.

Appropriate stability data have been generated to support a suitable retest period when stored in the proposed packaging.
P. Medicinal Product
Other Ingredients
Other ingredients consist of the pharmaceutical excipients docusate sodium, sodium laurilsulphate, carmellose calcium, pregelatinised maize starch, hydroxypropylcellulose, lactose monohydrate and magnesium stearate (E572). In addition the 16 mg and 32 mg strengths also contain iron oxide red (E172).

All excipients comply with their respective European Pharmacopoeia monographs with the exception of iron oxide red which complies with current EU directives concerning the use of colouring agents. Satisfactory certificates of analysis have been provided for all excipients. Suitable batch analysis data have been provided for each excipient.

With the exception of lactose monohydrate, none of the excipients contain materials of animal or human origin. The supplier of lactose monohydrate has confirmed that the lactose is sourced from healthy animals under the same conditions as milk 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 formulate stable, robust, tablets containing 4 mg, 8 mg, 16 mg or 32 mg candesartan cilexetil, which could be considered generic medicinal products of Atacand 4 mg, 8 mg, 16 mg and 32 mg tablets (AstraZeneca A/S).

A satisfactory account of the pharmaceutical development has been provided.

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

Manufacturing Process
Satisfactory batch formulae have been provided for the manufacture of product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specification
The proposed finished product specifications are acceptable. Test methods have been described and have been adequately validated. Batch data have been provided, which comply with the release specifications. Certificates of Analysis have been provided for all working standards used.

Container-Closure System
All strengths of the finished product are packaged in polyvinylchloride/polyvinylidene chloride/ aluminium blister strips in pack sizes of 7, 14, 28, 30, 50, 56, 70, 84, 90, 98 and 100 tablets. In addition, the 4 mg, 8 mg and 16 mg strengths are also available in a pack size of 250 tablets.

It has been stated that not all pack sizes may be marketed, however, the Marketing Authorisation Holder has committed to submitting the mock-ups for any pack size to the relevant regulatory authorities for approval before marketing.
Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

**Stability of the product**
Stability studies were performed in accordance with current guidelines on batches of finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 2 years with the storage conditions ‘Do not store above 25ºC’ (4 mg and 8 mg strengths) or ‘Do not store above 30ºC’ (16 mg and 32 mg).

**Bioequivalence/bioavailability**
Satisfactory certificates of analysis have been provided for the test and reference batches used in the bioequivalence study.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels**
The SmPCs, PIL and labels are acceptable.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups (‘user testing’), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet 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.

**Marketing Authorisation Application (MAA) form**
The MAA forms are satisfactory.

**Expert report**
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

**Conclusion**
There are no objections to the approval of these products from a pharmaceutical viewpoint.

**III.2 NON-CLINICAL ASPECTS**
As the pharmacodynamic, pharmacokinetic and toxicological properties of candesartan cilexetil are well-known, no new non-clinical studies are required and none have been provided.

The applicant’s non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant pharmacology and toxicology.

Suitable justification has been provided for non-submission of an environmental risk assessment. As these products are intended for generic substitution with other products already on the market, it is not considered to increase the environmental risk. Thus, the applicant’s justification is accepted.

There are no objections to the approval of these products from a non-clinical viewpoint.
III.3 CLINICAL ASPECTS
Pharmacokinetics
In support of these applications, the marketing authorisation holder has submitted the following two bioequivalence studies:

STUDY 1
An open label, randomised, single-dose, two-way, crossover, study to compare the pharmacokinetics of the test product Candesartan cilexetil 8 mg Tablets (Arrow Generics Limited) versus the reference product Atacand 8 mg tablets (AstraZeneca, France) in healthy adult volunteers under fasted conditions.

All volunteers received a single oral dose of either the test or reference product as a 1 x 8 mg tablet administered under fasting conditions. Blood samples were taken for the measurement of pharmacokinetic parameters at pre- and up to 48 hours post dose. The washout period between treatment periods was at least 7 days.

The pharmacokinetic results for candesartan are presented below (log-transformed values; geometric least squares mean, ratios and 90% confidence intervals):

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC$_{0-t}$ ng/ml/h</th>
<th>AUC$_{0-\infty}$ ng/ml/h</th>
<th>C$_{\text{max}}$ ng/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test (mean)</td>
<td>635.68</td>
<td>663.50</td>
<td>69.33</td>
</tr>
<tr>
<td>Reference (mean)</td>
<td>592.65</td>
<td>618.88</td>
<td>64.88</td>
</tr>
<tr>
<td>Ratio (90% CI)</td>
<td>107.25</td>
<td>106.99</td>
<td>106.60</td>
</tr>
</tbody>
</table>

AUC$_{0-t}$ area under the plasma concentration-time curve from time zero to t hours
AUC$_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
C$_{\text{max}}$ maximum plasma concentration

STUDY 2
An open label, randomised, single-dose, two-way, crossover, study to compare the pharmacokinetics of the test product Candesartan cilexetil 32 mg Tablets (Arrow Generics Limited) versus the reference product Atacand 32 mg tablets (AstraZeneca, France) in healthy adult volunteers under fasted conditions.

All volunteers received a single oral dose of either the test or reference product as a 1 x 32 mg tablet administered under fasting conditions. Blood samples were taken for the measurement of pharmacokinetic parameters at pre- and up to 48 hours post dose. The washout period between treatment periods was at least 7 days.

The pharmacokinetic results for candesartan are presented below (log-transformed values; geometric least squares mean, ratios and 90% confidence intervals):

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC$_{0-t}$ ng/ml/h</th>
<th>AUC$_{0-\infty}$ ng/ml/h</th>
<th>C$_{\text{max}}$ ng/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test (mean)</td>
<td>3144.18</td>
<td>3307.95</td>
<td>270.47</td>
</tr>
<tr>
<td>Reference (mean)</td>
<td>3062.56</td>
<td>3211.05</td>
<td>273.82</td>
</tr>
<tr>
<td>Ratio (90% CI)</td>
<td>103.74</td>
<td>104.40</td>
<td>99.73</td>
</tr>
</tbody>
</table>

AUC$_{0-t}$ area under the plasma concentration-time curve from time zero to t hours
AUC$_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
C$_{\text{max}}$ maximum plasma concentration

The 90% confidence intervals for AUC and C$_{\text{max}}$ for test versus reference product for candesartan for both strengths are within predefined acceptance criteria specified in
"Guideline on the Investigation of Bioequivalence” (CPMP/EWP/QWP/1401/98 Rev 1/, Corr). Thus, the data support the claim that the test product is bioequivalent to the reference product.

As the 4 mg, 8 mg, 16 mg and 32 mg strengths of the product meet the criteria specified in “Guideline on the Investigation of Bioequivalence” (CPMP/EWP/QWP/1401/98 Rev 1/, Corr), the results and conclusions of the bioequivalence studies on the 8 mg and 32 mg strengths can be extrapolated to 4 mg and 16 mg strengths.

**Pharmacodynamics**
No new pharmacodynamic data were submitted and none were required for these applications.

**Efficacy**
No new efficacy data were submitted and none were required for these applications.

**Safety**
With the exception of the data generated during the bioequivalence studies, no new safety data were submitted and none were required for these applications. No new or unexpected safety issues were highlighted by the bioequivalence data.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels**
The SmPCs, PIL and labels are acceptable. The SmPCs are consistent with that for the originator products. The PIL is consistent with the SmPCs and in line with current guidelines. The labelling is in-line with current guidelines.

**Clinical Expert Report**
The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

**Pharmacovigilance System and Risk Management Plan**
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.

Suitable justification has been provided for not submitting a Risk Management Plan for these products.

**Conclusion**
There are no objections to the approval of these products from a clinical viewpoint.
IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The 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. The pharmacodynamic, pharmacokinetic and toxicological properties of candesartan cilexetil are well-known.

EFFICACY
With the exception of the bioequivalence studies, no new data were submitted and none are required for applications of this type.

Bioequivalence has been demonstrated between the applicant’s Candesartan cilexetil 8 mg and 32 mg Tablets and its respective reference product (Atacand 8 mg and 32 mg tablets, AstraZeneca, France). As the 4 mg, 8 mg, 16 mg and 32 mg strengths of the product meet the biowaiver criteria specified in “Guideline on the Investigation of Bioequivalence” (CPMP/EWP/QWP/1401/98 Rev 1/, Corr), the results and conclusions of the bioequivalence studies on the 8 mg and 32 mg strengths can be extrapolated to the 4 mg and 16 mg strengths.

SAFETY
With the exception of the bioequivalence studies, no new data were submitted and none are required for applications of this type. As the safety profile of candesartan cilexetil is well-known, no additional data were required. No new or unexpected safety concerns arose from the safety data from the bioequivalence studies.

PRODUCT LITERATURE
The SmPCs, PIL and labelling are satisfactory and consistent with that for the reference products, where appropriate, in line with current guidelines.

BENEFIT-RISK ASSESSMENT
The quality of the products is acceptable and no new non-clinical or clinical safety concerns have been identified. The bioequivalence studies support the claim that the applicant’s products and the originator products are interchangeable. Extensive clinical experience with candesartan cilexetil is considered to have demonstrated the therapeutic value of the compound. The benefit-risk is, therefore, considered to be positive.
## Module 6

### STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>