Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Catasart 32 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 32 mg of candesartan cilexetil
Excipient: each tablet contains 278.27 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.

Catasart 32 mg tablets: pink, mottled, round biconvex tablet, debossed with 32 in one side and scored on the other side.

The tablet can be divided into equal halves.The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Catasart is indicated for the:

- Treatment of essential hypertension in adults and children and adolescents aged 6 to < 18 years.
- The treatment of adult patients with heart failure and impaired left ventricular systolic function (left ventricular ejection fraction ≤ 40%) when ACE-inhibitors are not tolerated or as add-on therapy to ACE-inhibitors in patients with symptomatic heart failure, despite optimal therapy, when mineralocorticoid receptor antagonists are not tolerated (see sections 4.2, 4.4, 4.5 and 5.1).

4.2 Posology and method of administration

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.
Catasart may also be administered with other antihypertensive agents (see sections 4.3, 4.4, 4.5 and 5.1). Addition of hydrochlorothiazide has been shown to have an additive antihypertensive effect with various doses of Catasart.

Elderly population
No initial dose 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. Catasart 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 Catasart and concomitant therapy may be more frequently needed for blood pressure control in black patients than in non-black patients (see section 5.1).

Paediatric population
Children and adolescents aged 6 to <18 years:
The recommended starting dose is 4 mg once daily.

- For patients weighing < 50 kg: In patients whose blood pressure is not adequately controlled, the dose can be increased to a maximum of 8 mg once daily.

- For patients weighing ≥ 50 kg: In patients whose blood pressure is not adequately controlled, the dose can be increased to 8 mg once daily and then to 16 mg once daily if needed (see section 5.1).

Doses above 32 mg have not been studied in paediatric patients.

Most of the antihypertensive effect is attained within 4 weeks.

For children with possible intravascular volume depletion (e.g., patients treated with diuretics, particularly those with impaired renal function), Catasart treatment should be initiated under close medical supervision and a lower starting dose than the general starting dose above should be considered (see section 4.4).

Candesartan has not been studied in children with glomerular filtration rate less than 30 ml/min/1.73m2 (see section 4.4).

Black paediatric patients
The antihypertensive effect of candesartan is less pronounced in black patients than in nonblack patients (see section 5.1).

Children aged below 1 year to <6 years
- The safety and efficacy in children aged 1 to <6 years of age has not been established. Currently available data are described in section 5.1 but no recommendation on a posology can be made.

- Catasart is contraindicated in children aged below 1 year (see section 4.3).

Posology in Heart Failure

The usual recommended initial dose of Catasart 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.
Catasart can be administered with other heart failure treatment, including ACE-inhibitors, beta-blockers, diuretics and digitalis or a combination of these medicinal products. Catasart may be co-administered with an ACE-inhibitor in patients with symptomatic heart failure despite optimal standard heart failure therapy when mineralocorticoid receptor

antagonists are not tolerated. The combination of an ACE-inhibitor, a potassium-sparing diuretic and Catasart 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 Catasart in children aged between birth and 18 years have not been established in the treatment of hypertension and heart failure. No data are available.

Method of administration

Oral use.
Catasart 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 trimester of pregnancy (see section 4.4 and 4.6).
- Severe hepatic impairment and/or cholestasis.
- The concomitant use of Catasart with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m^2) (see sections 4.5 and 5.1).
- Children aged below 1 year (see section 5.3).

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 Catasart.

When Catasart 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 Catasart 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 Catasart, 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 events, especially hypotension, hyperkalaemia and decreased renal function (including acute renal failure), may increase when Catasart is used in combination with an ACE inhibitor (see section 4.8). Triple combination of an ACE-inhibitor, a mineralocorticoid receptor antagonist and candesartan is also not recommended. Use of these combinations should be under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure.

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

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)

There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended (see sections 4.5 and 5.1).
If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure.
ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

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 Catasart 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 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 Catasart in patients with a recent kidney transplantation.

Hypotension
Hypotension may occur during treatment with Catasart in heart failure patients. It may also occur in hypertensive patients with intravascular volume depletion such as those receiving high dose diuretics.
Caution should be observed when initiating therapy and correction of hypovolemia should be attempted.

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

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

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

Hyperkalaemia
Concomitant use of Catasart 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 Catasart, hyperkalaemia may occur. Periodic monitoring of serum potassium is recommended.
The combination of an ACE inhibitor, a potassium-sparing diuretic (e.g. spironolactone) and Catasart is not recommended and should be considered only after careful evaluation of the potential benefits and risks.

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

cerebrovascular disease could result in a myocardial infarction or stroke.

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

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

Use in paediatric patients, including patients with renal impairment
Candesartan has not been studied in children with a glomerular filtration rate less than 30 ml/min/1.73m2 (see section 4.2).

For children with possible intravascular volume depletion (e.g. patients treated with diuretics, particularly those with impaired renal function), Catasart treatment should be initiated under close medical supervision and a lower starting dose should be considered (see section 4.2).

In post-menarche patients the possibility of pregnancy should be evaluated on a regular basis.
Appropriate information should be given and/or action taken to prevent the risk of exposure during pregnancy (see sections 4.3 and 4.6).

Special warnings regarding excipients
Catasart contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

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).

Dual blockade of the RAAS with AIIRAs, ACE inhibitors, or aliskiren
Clinical trial data has shown that dual blockade of the renin-angiotensin-aldosterone-system (RAAS) through the combined use of ACE inhibitors, angiotensin II receptor blockers or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting agent (see sections 4.3, 4.4 and 5.1).

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors. A similar effect may occur with AIIRAs. Use of candesartan with lithium is not recommended. If the combination proves necessary, careful monitoring of serum lithium levels is recommended.

When AIIRAs are administered simultaneously with 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.

Paediatric population
Interaction studies have only been performed in adults.

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 2nd and 3rd trimester 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 is no controlled epidemiological data on the risk with AIIRAs, similar risks may exist for this class of drugs. Unless continued AIIRAtherapy 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 section5.3).
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 Catasart during breastfeeding, Catasart is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.

4.7 Effects on ability to drive and use machines

No studies on the effects 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 Catasart.

4.8 Undesirable effects

Treatment of Hypertension

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

In a pooled analysis of clinical trial data of hypertensive patients, adverse reactions with candesartan cilexetil were defined based on an incidence of adverse events with candesartan cilexetil at least 1% higher than the incidence seen with placebo. By this definition, the most commonly reported adverse reactions were dizziness/vertigo, headache and respiratory infection.

The table below presents adverse reactions from clinical trials and post-marketing experience.
The frequencies used in the tables throughout this section are:
Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

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

Laboratory findings

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

Treatment of Heart Failure

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

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

System Organ Class	Frequency	Undesirable Effect
Blood and lymphatic system disorders	Very rare	Leukopenia, neutropenia and agranulocytosis
Metabolism and nutrition		

disorders	Common	Hyperkalaemia
	Very rare	Hyponatraemia
Nervous system disorders	Very rare	Dizziness, headache
Vascular disorders	Common	Hypotension
Respiratory, thoracic and mediastinal disorders	Very rare	Cough
Gastrointestinal disorders	Very rare	Nausea
Hepato-biliary disorders	Very rare	Increased liver enzymes, abnormal hepatic function or hepatitis
Skin and subcutaneous tissue disorders	Very rare	Angioedema, rash, urticaria, pruritus
Musculoskeletal and connective tissue disorders	Very rare	Back pain, arthralgia, myalgia
Renal and urinary disorders	Common	Renal impairment, including renal failure in susceptible patients (see section 4.4)

Laboratory findings:

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

Paediatric population

The safety of candesartan cilexetil was monitored in 255 hypertensive children and adolescents, aged 6 to <18 years old, during a 4 week clinical efficacy study and a 1 year open label study (see section 5.1). In nearly all different system organ classes, the frequency of adverse events in children are within common/uncommon range. Whilst the nature and severity of the adverse events are similar to those in adults (see the table above), the frequency of all adverse events are higher in children and adolescent, particularly in:

- Headache, dizziness and upper respiratory tract infection, are “very common” (ie, ≥1/10) in children and common (≥ 1/100 to < 1/10) in adults.
- Cough is “very common” (ie, > 1/10) in children and very rare (<1/10,000) in adults.
- Rash is “common” (ie, ≥1/100 to <1/10) in children and “very rare” (<1/10,000) in adults.
- Hyperkalemia, hyponatraemia and abnormal liver function are uncommon (≥ 1/1,000 to < 1/100) in children and very rare (< 1/10,000) in adults.
- Sinus arrhythmia, nasopharyngitis, pyrexia are “common” (ie, ≥1/100 to <1/10) and oropharyngeal pain is “very common” (ie, ≥1/10) in children; but none are reported in adults. However these are temporary and widespread childhood illnesses.

The overall safety profile for candesartan cilexetil in paediatric patients does not differ significantly from the safety profile in adults.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; e-mail: medsafety@hpra.ie

4.9 Overdose

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

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Angiotensin II is the primary vasoactive hormone of the renin-angiotensin-aldosterone system and plays a role in the pathophysiology of hypertension, heart failure and other cardiovascular disorders. It also has a role in the pathogenesis of end organ hypertrophy and damage. The major physiological effects of angiotensin II, such as vasoconstriction, aldosterone stimulation, regulation of salt and water homeostasis and stimulation of cell growth, are mediated via the type 1 (AT1) 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 AT1 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 cilexetil with ACE inhibitors, the incidence of cough was lower in patients receiving candesartan cilexetil. Candesartan does not bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation. The antagonism of the angiotensin II (AT1) 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% CI15-42%). There is currently no data on the effect of candesartan on the progression to diabetic nephropathy.

The effects of candesartan cilexetil 8-16 mg (mean 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 cilexetil 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).

Paediatric population
The antihypertensive effects of candesartan were evaluated in hypertensive children aged 1 to <6 years and 6 to <17 years in two randomised, double-blind multicentre, 4 week dose ranging studies.

In children aged 1 to <6 years, 93 patients, 74% of whom had renal disease, were randomized to receive an oral dose of candesartan cilexetil suspension 0.05, 0.20 or 0.40 mg/kg once daily.
The primary method of analysis was slope of the change in systolic blood pressure (SBP) as a function of dose. SBP and diastolic blood pressure (DBP) decreased 6.0/5.2 to 12.0/11.1 mmHg from baseline across the three doses of candesartan cilexetil. However, since there was no placebo group, the true magnitude of blood pressure effect remains uncertain which makes a conclusive assessment of benefit-risk balance difficult in this age group.

In children aged 6 to <17 years, 240 patients were randomised to receive either placebo or low, medium, or high doses of candesartan cilexetil in a ratio of 1: 2: 2: 2. For children who weighed < 50 kg, the doses of candesartan cilexetil were 2, 8, or 16 mg once daily. In children who weighed > 50 kg, the candesartan cilexetil doses were 4, 16 or 32 mg once daily. Candesartan at pooled doses reduced SiSBP by 10.22 mmHg (P< 0.0001) and SiDBP (P=0.0029) by 6.56 mmHg, from the base line. In the placebo group, there was also a reduction of 3.667 mmHg in SiSBP (p=0.0074) and 1.80 mmHg for SiDBP (p=0.0992) from the baseline. Despite the large placebo effect, all individual candesartan doses (and all doses pooled) were significantly superior to placebo. Maximum response in reduction of blood pressure in children below and above 50 kg was reached at 8mg and 16 mg doses, respectively and the effect plateaued after that point.

Of those enrolled, 47% were black patients and 29% were female; mean age +/- SD was 12.9 +/- 2.6 years. In children aged 6 to < 17 years there was a trend for a lesser effect on blood pressure in black patients compared to non-black patients.

Heart Failure

Treatment with candesartan cilexetil reduces mortality, reduces hospitalisation due to heart failure and improves

symptoms in patients with left ventricular systolic dysfunction as shown in the Candesartan in Heart failure – Assessment of Reduction in Mortality and morbidity (CHARM) programme.

This placebo controlled, double-blind study programme in chronic heart failure (CHF) patients with NYHA functional class II to IV consisted of three separate studies: CHARM-Alternative (n=2,028) in patients with LVEF ≤40% not treated with an ACE inhibitor because of intolerance (mainly due to cough, 72%), CHARM-Added (n=2,548) in patients with LVEF ≤ 40% and treated with an ACE inhibitor, and CHARM-Preserved (n=3,023) in patients with LVEF>40%. Patients on optimal CHF therapy at baseline were randomised to placebo or candesartan cilexetil (titrated from 4 mg or 8 mg once daily to 32 mg once daily or the highest tolerated dose, mean dose 24 mg) and followed for a median of 37.7 months. After 6 months of treatment 63% of the patients still taking candesartan cilexetil (89%) were at the target dose of 32 mg.

In CHARM-Alternative, the composite endpoint of cardiovascular mortality or first CHF hospitalisation was significantly reduced with candesartan in comparison with placebo,hazard ratio (HR) 0.77(95% CI 0.67-0.89, p<0.001). This corresponds to a relative risk reduction of 23%. Of candesartan patients 33.0% (95%CI: 30.1 to 36.0) and of placebo patients 40.0% (95%CI: 37.0 to 43.1) experienced this endpoint, absolute difference 7.0% (95%CI: 11.2 to 2.8). Fourteen patients needed to be treated for the duration of the study to prevent one patient from dying of a cardiovascular event or being hospitalised for treatment of heart failure. The composite endpoint of all-cause mortality or first CHF hospitalisation was also significantly reduced with candesartan HR 0.80(95%CI: 0.70-0.92, p=0.001). Of candesartan patients 36.6% (95%CI: 33.7 to 39.7) and of placebo patients 42.7% (95%CI: 39.6 to 45.8) experienced this endpoint, absolute difference 6.0% (95%CI: 10.3 to 1.8).
Both the mortality and morbidity (CHF hospitalisation) components of these composite endpoints contributed to the favourable effects of candesartan . Treatment with candesartan cilexetil resulted in improved NYHA functional class (p=0.008).

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

In CHARM-Preserved, no statistically significant reduction was achieved in the composite endpoint of cardiovascular mortality or first CHF hospitalisation, HR 0.89(95%CI: 0.77-1.03, p=0.118).

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

The beneficial effects of candesartan were consistent irrespective of age, gender and concomitant medication. Candesartan was effective also in patients taking both beta-blockers and ACE inhibitors at the same time, and the benefit was obtained whether or not patients were taking ACE inhibitors at the target dose recommended by treatment guidelines.

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

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)
Two large randomised, controlled trials (ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) and VA NEPHRON-D (The Veterans Affairs Nephropathy in Diabetes)) have examined the use

of the combination of an ACE-inhibitor with an angiotensin II receptor blocker.
ONTARGET was a study conducted in patients with a history of cardiovascular or cerebrovascular disease, or type 2 diabetes mellitus accompanied by evidence of end-organ damage. VA NEPHRON-D was a study in patients with type 2 diabetes mellitus and diabetic nephropathy.
These studies have shown no significant beneficial effect on renal and/or cardiovascular outcomes and mortality, while an increased risk of hyperkalaemia, acute kidney injury and/or hypotension as compared to monotherapy was observed. Given their similar pharmacodynamic properties, these results are also relevant for other ACE-inhibitors and angiotensin II receptor blockers.
ACE-inhibitors and angiotensin II receptor blockers should therefore not be used concomitantly in patients with diabetic nephropathy.
ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints) was a study designed to test the benefit of adding aliskiren to a standard therapy of an ACE-inhibitor or an angiotensin II receptor blocker in patients with type 2 diabetes mellitus and chronic kidney disease, cardiovascular disease, or both. The study was terminated early because of an increased risk of adverse outcomes. Cardiovascular death and stroke were both numerically more frequent in the aliskiren group than in the placebo group and adverse events and serious adverse events of interest (hyperkalaemia, hypotension and renal dysfunction) were more frequently reported in the aliskiren group than in the placebo group.

5.2 Pharmacokinetic properties

Absorption and distribution

Following oral administration, candesartan cilexetil is converted to the active substance candesartan. The absolute bioavailability of candesartan is approximately 40% after an oral solution of candesartan cilexetil. The relative bioavailability of the tablet formulation compared with the same oral solution is approximately 34% with very little variability. The estimated absolute bioavailability of the tablet is therefore 14%. The mean peak serum concentration (C_{max}) is reached 3-4 hours following tablet intake. The candesartan serum concentrations increase linearly with increasing doses in the therapeutic dose range. No gender related differences in the pharmacokinetics of candesartan have been observed. The area under the serum concentration versus time curve (AUC) of candesartan is not significantly affected by food.
Candesartan is highly bound to plasma protein (more than 99%). The apparent volume of distribution of candesartan is 0.1 l/kg.

The bioavailability of candesartan is not affected by food.

Biotransformation and elimination

Candesartan is mainly eliminated unchanged via urine and bile and only to a minor extent eliminated by hepatic metabolism (CYP2C9). Available interaction studies indicate no effect on CYP2C9 and CYP3A4. Based on *in vitro* data, no interaction would be expected to occur *in vivo* with drugs whose metabolism is dependent upon cytochrome P450 isoenzymes CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1 or CYP3A4. The terminal half-life of candesartan is approximately 9 hours. There is no accumulation following multiple doses.

Total plasma clearance of candesartan is about 0.37 ml/min/kg, with a renal clearance of about 0.19 ml/min/kg. The renal elimination of candesartan is both by glomerular filtration and active tubular secretion. Following an oral dose of ^{14}C-labelled candesartan cilexetil, approximately 26% of the dose is excreted in the urine as candesartan and 7% as an inactive metabolite while approximately 56% of the dose is recovered in the faeces as candesartan and 10% as the inactive metabolite.

Pharmacokinetics in special populations

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

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

In two studies, both including patients with mild to moderate hepatic impairment, there was an increase in the mean AUC of candesartan of approximately 20% in one study and 80% in the other study (see section 4.2). There is no experience in patients with severe hepatic impairment.

Paediatric population
The pharmacokinetic properties of candesartan were evaluated in hypertensive children aged 1 to <6 years and 6 to <17 years in two single dose PK studies.

In children aged 1 to <6 years, 10 children weighting 10 to <25 kg received a single dose of 0.2 mg/kg, oral suspension. There was no correlation between Cmax and AUC with age or weight.
No clearance data has been collected; therefore the possibility of a correlation between clearance and weight/age in this population is unknown.

In children aged 6 to <17 years, 22 children received a single dose of 16 mg tablet. There was no correlation between Cmax and AUC with age. However weight seems to significantly correlate with Cmax (p=0.012) and AUC (p=0.011). No clearance data, has been collected, therefore the possibility of a correlation between clearance and weight/age in this population is unknown.

Children >6 years of age had exposure similar to adults given the same dose.

The pharmacokinetics of candesartan cilexetil have not been investigated in paediatric patients <1 year of age.

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.

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

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

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

Data from *in vitro* and *in vivo* mutagenicity testing indicate that candesartan will not exert mutagenic or clastogenic activities under conditions of clinical use.

There was no evidence of carcinogenicity.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Maize starch
Povidone K-30
Carrageenan
Croscarmellose sodium
Magnesium stearate
Iron oxide, red (E172)
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

HDPE bottles: use within 3 months after first opening

6.4 Special precautions for storage

Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Al/Al Blister: 7, 10, 14, 28, 30, 56, 98, 100, 300 tablets
Al/Al Blister with desiccant: 7, 10, 14, 28, 30, 56, 98, 100, 300 tablets
HDPE bottle with PP cap and silica gel desiccant: 30, 100, 500 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements

7 MARKETING AUTHORISATION HOLDER

Rowex Ltd
Bantry
Co. Cork
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0711/134/004

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 4th September 2009
Date of last renewal: 30th April 2012

10 DATE OF REVISION OF THE TEXT

September 2015