

## CANDESARTAN VIATRIS

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### 1. Product Name

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Candesartan Viatriis, 4 mg, 8 mg, 16 mg and 32 mg tablets.

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### 2. Qualitative and Quantitative Composition

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Each tablet contains 4 mg, 8 mg, 16 mg or 32 mg of candesartan cilexetil.

Excipients with known effect: Contains sugars as lactose.

For the full list of excipients, see section 6.1.

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### 3. Pharmaceutical Form

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Candesartan Viatriis 4 mg: White to off-white, round tablets with approximately 7 mm of diameter, with a score line on one face and a “4” on the other face.

Candesartan Viatriis 8 mg: Round tablets with approximately 6.4 mm of diameter, non-uniform pink colour (with possible darker colour or white spots) with a score line on one face and a “8” on the other face.

Candesartan Viatriis 16 mg: Round tablets of approximately 7 mm diameter, non-uniform pink colour (with possible darker colour or white spots) with a score line on one face and a “16” on the other face.

Candesartan Viatriis 32 mg: Round tablets of approximately 9.5 mm diameter, non-uniform pink colour (with possible darker colour or white spots) with a score line on one face and a “32” on the other face.

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### 4. Clinical Particulars

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#### 4.1 *Therapeutic indications*

- Hypertension
- Treatment of patients with heart failure and left ventricular systolic dysfunction. Treatment with candesartan cilexetil reduces mortality, reduces hospitalisation due to heart failure, and improves symptoms.

#### 4.2 *Dose and method of administration*

##### **Dosage in hypertension**

The recommended initial and maintenance dose of Candesartan Viatriis is 8 mg once daily. The dose may be increased to 16 mg once daily. In patients who require further blood pressure reduction, the dose may be increased to 32 mg once daily.

Therapy should be adjusted according to blood pressure response. The maximal antihypertensive effect is attained within 4 weeks after initiation of treatment.

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In patients with less than optimal blood pressure reduction on Candesartan Viatris, combination with a thiazide diuretic is recommended.

### **Use in the elderly**

No initial dosage adjustment is necessary for elderly patients.

### **Use in impaired renal function**

No initial dosage adjustment is necessary in patients with mild to moderate impaired renal function (i.e. creatinine clearance  $\geq 30$ -80 mL/min/1.73 m<sup>2</sup> BSA). In patients with severe impaired renal function (i.e. creatinine clearance  $< 30$  mL/min/1.73 m<sup>2</sup> BSA), including patients on haemodialysis a lower initial dose of 4 mg should be considered.

### **Use in impaired hepatic function**

Patients with hepatic impairment: Dose titration is recommended in patients with mild to moderate chronic liver disease, and a lower initial dose of 4 mg should be considered. Candesartan Viatris should not be used in patients with severe hepatic impairment and/or cholestasis (see section 4.3).

### **Concomitant therapy**

Candesartan Viatris may be administered with other antihypertensive agents (see section 5.1)

### **Dosage in heart failure**

The usual recommended initial dose for Candesartan Viatris is 4 mg once daily. Up-titration to the target dose of 32 mg once daily or the highest tolerated dose is done by doubling the dose at intervals of at least 2 weeks (see section 4.4).

### **Concomitant therapy**

Candesartan Viatris can be administered with other heart failure treatment, including ACE inhibitors, beta-blockers, diuretics and digitalis or a combination of these medicinal products (see section 4.4 and 5.2).

### **Method of administration**

Candesartan Viatris should be taken once daily with or without food.

### **Use in Children**

The safety and efficacy of Candesartan Viatris have not been established in children.

## **4.3 Contraindications**

Hypersensitivity to any component present in Candesartan Viatris tablets.

Pregnancy and lactation.

Severe hepatic impairment and/or choleostasis.

The use of candesartan cilexetil in combination with aliskiren-containing medicines in patients with diabetes mellitus (type I or II) or moderate to severe renal impairment (GFR  $< 60$  mL/min/1.73 m<sup>2</sup>).

## **4.4 Special warnings and precautions for use**

### **Hypotension**

Hypotension may occur during treatment with candesartan cilexetil in heart failure patients. As described for other agents acting on the renin-angiotensin-aldosterone system, it may also occur in hypertensive patients with intravascular volume depletion. Caution should be observed when initiating therapy and correction of hypovolaemia should be attempted.

## **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 candesartan cilexetil with an ACE-inhibitor or aliskiren is therefore not recommended (see section 4.5).

If dual blockade therapy is considered 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. The use of candesartan cilexetil with aliskiren is contraindicated in patients with diabetes mellitus (type I or II) or moderate to severe renal impairment ( $GFR < 60 \text{ ml/min/1.73 m}^2$ ) (see section 4.3).

## **Use in heart failure**

Triple combination of candesartan cilexetil with an ACE-inhibitor and a mineralocorticoid receptor antagonist used in heart failure 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.

## **Renal artery stenosis**

Other drugs that affect the renin-angiotensin-aldosterone system, i.e. angiotensin converting enzyme (ACE) inhibitors, may increase blood urea and serum creatinine in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney. A similar effect may be anticipated with angiotensin II receptor antagonists.

## **Renal impairment**

As with other agents inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible patients treated with candesartan cilexetil.

When candesartan cilexetil is used in hypertensive patients with severe renal impairment, periodic monitoring of serum potassium and creatinine levels should be considered. There is very limited experience in patients with very severe or end-stage renal impairment (i.e. creatinine clearance  $< 15 \text{ mL/min/1.73 m}^2 \text{ BSA}$ ).

Evaluation of patients with heart failure should include periodic assessments of renal function. During dose titration of candesartan cilexetil, monitoring of serum creatinine and potassium is recommended.

## **Kidney transplantation**

There is limited clinical experience regarding candesartan cilexetil use in patients who have undergone renal transplant.

## **Haemodialysis**

During dialysis the blood pressure may be particularly sensitive to  $AT_1$ -receptor blockade as a result of reduced plasma volume and activation of the renin-angiotensin-aldosterone system. Therefore, candesartan cilexetil should be carefully titrated with thorough monitoring of blood pressure in patients on haemodialysis (see section 4.2).

## **Hepatic impairment**

There is limited experience in patients with severe hepatic impairment and/or cholestasis. Use in patients with severe hepatic impairment is contraindicated. Caution is advised in patients with mild to moderate hepatic impairment. There have been reports of clinically significant liver disease occurring with other angiotensin II receptor antagonists. No such cases have been reported to date with candesartan.

## **Aortic and mitral valve stenosis (or 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.

## **Hyperkalaemia**

Based on experience with the use of other drugs that affect the renin-angiotensin-aldosterone system, concomitant use of potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium or other drugs that may increase potassium levels (e.g. heparin, cotrimoxazole) may lead to increases in serum potassium in hypertensive patients.

In heart failure patients treated with candesartan cilexetil, hyperkalaemia may occur. During treatment with candesartan cilexetil in patients with heart failure, periodic monitoring of serum potassium is recommended, especially when taken concomitantly with ACE inhibitors and potassium-sparing diuretics such as spironolactone.

## **Anaesthesia and surgery**

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

## **Angioedema**

Angioedema including swelling of the face, lips, throat, tongue and the intestines (see section 4.4 – intestinal angioedema) has been reported rarely in patients treated with angiotensin II receptor antagonists. Some of these patients previously experienced angioedema with other medicines, including ACE inhibitors. The risk of developing angioedema is lower for angiotensin II receptor antagonists compared to ACE inhibitors.

## **Intestinal angioedema**

Intestinal angioedema has been reported in patients treated with angiotensin II receptor antagonists, including candesartan (see section 4.8). As the risk of angioedema with angiotensin II receptor antagonist is lower compared to ACE inhibitors, the risk of intestinal angioedema is also presumed to be lower.

Patients with intestinal angioedema can present with non-specific gastrointestinal symptoms such as abdominal pain, nausea, vomiting and diarrhoea. Symptoms resolved after discontinuation of angiotensin II receptor antagonists. If intestinal angioedema is suspected, candesartan should be discontinued and appropriate monitoring should be initiated until complete resolution of symptoms has occurred.

## **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 drugs that affect this system has been associated with acute hypotension, azotaemia, oliguria or, rarely, acute renal failure.

As with any antihypertensive agent, excessive blood pressure decrease in patients with ischaemic heart disease or atherosclerotic cerebrovascular disease could result in a myocardial infarction or stroke.

## **Primary hyperaldosteronism**

Patients with primary hyperaldosteronism will not generally respond to antihypertensive drugs acting through inhibition of the renin-angiotensin-aldosterone system. Therefore, the use of candesartan in these patients is not recommended.

## **Combination use of ACE inhibitors or angiotensin receptor antagonists, anti-inflammatory drugs and thiazide diuretics**

The use of an ACE inhibiting drug (ACE-inhibitor or angiotensin receptor antagonist), an anti-inflammatory drug (NSAID or COX-2 inhibitor) and a thiazide diuretic at the same time increases the risk of renal impairment. This includes use in fixed-combination products containing more than one class of drug. Combined use of these medications should be accompanied by increased monitoring of serum creatinine, particularly at the institution of the combination. The combination of drugs from these three classes should be used with caution particularly in elderly patients or those with pre-existing renal impairment.

### **Paediatric use**

No data available.

### **Effects on laboratory tests**

#### ***Hypertension***

In general there were no clinically important effects of candesartan cilexetil on routine laboratory variables. As for other inhibitors of the renin-angiotensin-aldosterone system, small decreases in haemoglobin have been seen. In clinical trials, elevation of ALT occurred in 1.3% of candesartan-treated patients and 0.5% of those treated with placebo. The incidence of AST elevation was 0.4% with candesartan and 0% with placebo. No routine monitoring of laboratory variables is necessary for patients receiving candesartan cilexetil. However, in patients with severe renal impairment, periodic monitoring of serum potassium and creatinine levels should be considered.

#### ***Heart Failure***

Increases in creatinine, urea and potassium. Periodic monitoring of serum creatinine and potassium is recommended (see section 4.4).

## **4.5 Interaction with other medicines and other forms of interaction**

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

The combination of candesartan with aliskiren-containing medicine is contraindicated in patients with diabetes mellitus (type I or II) or moderate to severe renal impairment ( $GFR < 60 \text{ml/min/1.73m}^2$ ) and is not recommended in other patients. Clinical trial data has shown that dual blockade of the 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 section 4.3 and 4.4).

### **Lithium**

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 angiotensin II receptor antagonists (AIIIRAs) and careful monitoring of serum lithium levels is recommended during concomitant use.

### **Other drugs**

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

The antihypertensive effect of angiotensin II receptor antagonists, including candesartan may be attenuated by NSAIDs; including selective COX-2 inhibitors and acetylsalicylic acid.

As with ACE inhibitors, concomitant use of AIIIRAs 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 older patients and in volume depleted patients. Patients should be adequately hydrated and consideration should be given to monitoring renal function after initiation of concomitant therapy and periodically thereafter.

Candesartan is eliminated only to a minor extent by hepatic metabolism (CYP2C9). Available interaction studies indicate no effect on CYP2C9 and CYP3A4 but the effect on other cytochrome P450 isoenzyme is presently unknown.

The antihypertensive effect of candesartan cilexetil may be enhanced by other antihypertensives.

## **Food**

Food increases the rate of absorption of candesartan however, the extent of absorption of candesartan is not affected by food.

## **4.6 Fertility, pregnancy and lactation**

### **Pregnancy**

The use of candesartan cilexetil is contraindicated during pregnancy (see section 4.3). Patients receiving candesartan should be made aware of that before contemplating a possibility of becoming pregnant so that they can discuss appropriate options with their treating physician. When pregnancy is diagnosed, treatment with candesartan cilexetil must be stopped immediately and if appropriate, alternative therapy should be started.

When used in pregnancy, medicines that act directly on the renin-angiotensin system can cause foetal and neonatal injury and death. Exposure to angiotensin II receptor antagonist therapy is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia) (see section 5.3).

### **Breastfeeding**

It is not known whether candesartan cilexetil is excreted in human milk. However, candesartan is excreted in the milk of lactating rats. Because of the potential for adverse effects on the nursing infant, breast feeding should be discontinued if the use of candesartan cilexetil is considered essential (see section 4.3).

### **Fertility**

Candesartan cilexetil had no adverse effects on the reproductive performance of male or female rats at oral doses up to 300 mg/kg/day.

## **4.7 Effects on ability to drive and use machines**

The effect of candesartan cilexetil on the ability to drive and use machines has not been studied, but based on its pharmacodynamic properties candesartan cilexetil is unlikely to affect this ability. When driving vehicles or operating machines, it should be taken into account that dizziness or weariness may occur during treatment.

## **4.8 Undesirable effects**

### **Treatment of hypertension**

Candesartan cilexetil was well tolerated in controlled clinical studies showing an adverse event profile comparable to that of placebo. Generally adverse events were mild and transient.

The overall incidence of adverse events showed no association with dose, age or gender. Withdrawals from treatment due to adverse events were similar with candesartan cilexetil (3.1%) and placebo (3.2%).

Information on adverse events was obtained from 39 Phase I to Phase III clinical studies, involving a

total of 5,464 subjects. Candesartan was administered as mono or combination therapy to 2,061 hypertensive patients. The crude frequency of the most commonly occurring adverse events, irrespective of causality, reported for those patients and the 573 placebo comparators are given below.

**Table 1:**

Adverse Event	Monotherapy Studies		Combination Studies		
	Placebo	Candesartan	Placebo	Candesartan	Candesartan + HCTZ
	(n=573)	(n=1388)	(n=205)	(n=444)	(n=673)
<b>Cardiovascular</b>					
peripheral oedema	0.7	1.3	1.0	1.6	0.1
<b>Gastrointestinal</b>					
nausea	1.4	2.2	0.5	1.1	1.0
abdominal pain	1.9	1.7	2.0	1.4	1.2
diarrhoea	2.3	1.6	1.5	0.9	0.7
vomiting	1.0	1.2	-	-	-
<b>Musculo-skeletal</b>					
back pain	1.2	4.0	1.0	2.3	2.4
<b>Nervous system</b>					
headache	10.7	10.9	4.9	4.1	1.7
dizziness	2.6	2.7	2.0	1.6	2.2
<b>Other</b>					
influenza-like symptoms	1.0	1.9	0.5	0.9	1.8
inflicted injury	0.9	1.7	-	-	-
fatigue	1.6	1.5	-	-	-
<b>Respiratory</b>					
URTI	3.9	6.1	2.0	2.3	1.0
bronchitis	2.6	1.9	2.0	0.7	0.9
coughing	1.8	1.9	2.0	1.1	0.9
pharyngitis	0.7	1.9	-	-	-
rhinitis	0.5	1.3	-	1.1	0.6

HCTZ = hydrochlorothiazide

Median (mean) duration of exposure: placebo 57 (68 days) and candesartan cilexetil: 56 (78 days).

## 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. Adverse reactions commonly ( $\geq 1/100$ ,  $< 1/10$ ) seen were:

### **Vascular disorders:**

Hypotension.

### **Metabolism and nutrition disorders:**

Hyperkalaemia.

### **Renal and urinary disorders:**

Renal impairment.

## **Post-marketing**

The following adverse reactions have been reported very rarely (< 1/10,000) in post marketing experience:

### ***Blood and lymphatic system disorders:***

Leukopenia, neutropenia and agranulocytosis.

### ***Metabolism and nutrition disorders:***

Hyperkalaemia, hyponatraemia.

### ***Hepato-biliary disorders:***

Increased liver enzymes, abnormal hepatic function or hepatitis.

### ***Gastrointestinal disorders:***

Intestinal angioedema.

### ***Skin and subcutaneous tissue disorders:***

Angioedema, rash, urticaria, pruritus.

### ***Musculoskeletal, connective tissue and bone disorders:***

Back pain, myalgia.

### ***Renal and urinary disorders:***

Renal impairment, including renal failure in susceptible patients (see section 4.4).

Rare reports of rhabdomyolysis have been reported in patients receiving angiotensin II receptor blockers.

Although causality to candesartan has not been established, palpitation has been very rarely reported as an adverse event during post-marketing surveillance. These were: agitation, anxiety, depression, insomnia, somnolence, nervousness, nightmare, sleep disorder and palpitations.

## **Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://pophealth.my.site.com/carmreportnz/s/>.

## **4.9 Overdose**

### **Symptoms**

Based on pharmacological considerations, the main manifestation of an overdose is likely to be symptomatic hypotension and dizziness.

In single case reports of overdose (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 drugs may be administered if the above-mentioned measures are not sufficient.

Candesartan cilexetil cannot be removed by haemodialysis.

For risk assessment and advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764 766).

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## 5. Pharmacological Properties

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### 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 significant role in the pathophysiology of hypertension, heart failure and other cardiovascular disorders. It also has an important 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<sub>1</sub>) receptor.

Candesartan cilexetil is a prodrug suitable for oral use. It is rapidly converted to the active drug, candesartan, by ester hydrolysis during absorption from the gastrointestinal tract. Candesartan is an angiotensin II receptor antagonist, selective for AT<sub>1</sub> 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. Since there is no effect on ACE and no potentiation of bradykinin or substance P, angiotensin II receptor antagonists are unlikely to be associated with cough. This has been confirmed in controlled clinical studies with candesartan cilexetil. Candesartan does not bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

In hypertension, candesartan cilexetil causes a dose-dependent, long-lasting reduction in arterial blood pressure. The antihypertensive action is due to decreased systemic peripheral resistance, while heart rate, stroke volume and cardiac output are not affected. There is no indication of serious or exaggerated first dose hypotension or rebound effect after cessation of treatment.

Candesartan is effective in hypertension. After administration of a single dose, onset of antihypertensive effect generally occurs within two hours. With continuous treatment, the maximum reduction in blood pressure with any dose is generally attained within four weeks and is sustained during long-term treatment. It provides effective and smooth blood flow pressure reduction over the 24 hours dosing interval, with a trough/peak ratio confirming once daily dosing.

Candesartan cilexetil can be used as monotherapy or in combination with other antihypertensive drugs, such as thiazide diuretics, dihydropyridine calcium antagonists and lisinopril, for improved blood pressure control. Age and gender have no influence on the efficacy of candesartan.

Candesartan has favourable renal haemodynamic effects. It increases renal blood flow and maintains or increases glomerular filtration rate while renal vascular resistance and filtration fraction are reduced. Candesartan reduces urinary protein excretion in hypertensive patients with microalbuminuria or nephropathy of different aetiology. Candesartan has no adverse effect on blood glucose or lipid profile. In a variety of preclinical safety studies conducted in several species, expected exaggerated pharmacological effects (e.g. renal changes leading to juxtaglomerular cell hypertrophy, adrenal gland zona glomerulosa atrophy and reduced heart weight related to reduced afterload), due to modification of the renin-angiotensin-aldosterone system homeostasis, have been observed. The incidence and severity of the effects induced were dose and time related and have been shown to be reversible in adult animals. Fetotoxicity has been observed in late pregnancy (see section 4.6).

### **Clinical efficacy and safety**

#### ***Hypertension***

The Candesartan and Lisinopril Microalbuminuria (CALM) study was a 24-week double blind, parallel

group trial (n=199) to evaluate the effects of candesartan and lisinopril alone and in combination on urinary albumin excretion (UAE) in patients with type II diabetes mellitus, hypertension and microalbuminuria. Patients were randomly allocated to four treatment regimens: 1) 24 weeks of candesartan monotherapy (1/3 of the patients); 2) 24 weeks of lisinopril monotherapy (1/3 of the patients); 3) 12 weeks of candesartan monotherapy, followed by 12 weeks of candesartan + lisinopril combination therapy (1/6 of the patients); and 4) 12 weeks of lisinopril monotherapy, followed by 12 weeks of lisinopril + candesartan combination therapy (1/6 of the patients). Thus, after 12 weeks, half of the patients were treated with candesartan monotherapy (n=99) and half with lisinopril monotherapy (n=98). After 24 weeks, 1/3 of the patients still in the study were on candesartan monotherapy (n=49), 1/3 on lisinopril monotherapy (n=46), and 1/3 on combination therapy (candesartan + lisinopril, n=25; lisinopril + candesartan, n=24).

**Table 2**

	Baseline		Change at 12 weeks		Change at 24 weeks	
	SBP mmHg	DBP mmHg	SBP mmHg	DBP mmHg	SBP mmHg	DBP mmHg
Candesartan 16 mg (n=49)	162	96	-15	-10	-14	-10
Lisinopril 20 mg (n=46)	161	96	-14	-10	-17	-11
Candesartan 16 mg + Lisinopril 20 mg from 12 weeks (n=25)	161	95	-16	-11	-22*	-16*
Lisinopril 20 mg + Candesartan 16 mg from 12 weeks (n=24)	161	96	-14	-10	-28***	-17***

\*p<0.05, \*\*\*p<0.001 for the additional blood pressure reduction at 24 weeks compared with 12 weeks

Significant reduction in urinary albumin/creatinine ratio (UACR), in both monotherapy treatment groups was observed, although no significant difference between treatment groups was seen.

Combination therapy following monotherapy for 12 weeks showed significantly greater reduction in UACR (mean reduction of 50%) than candesartan cilexetil 16 mg monotherapy (mean reduction in UACR 24%) and numerically greater reduction than lisinopril 20 mg monotherapy (mean reduction in UACR 39%).

All treatment regimens reduced both systolic and diastolic blood pressure significantly. The blood pressure reductions were significantly greater with combination therapy than with monotherapy, whether lisinopril was added to candesartan, or candesartan was added to lisinopril (see [Table 2](#)).

The antihypertensive effects of candesartan cilexetil and losartan potassium at their highest recommended doses administered once daily were compared in two randomised, double-blind trials. In a total of 1,268 patients with mild to moderate hypertension who were not receiving other antihypertensive therapy, candesartan cilexetil 32 mg lowered systolic and diastolic blood pressure by 2 to 3 mmHg on average more than losartan potassium 100 mg, when measured at the time of either peak or trough effect.

### **Heart Failure**

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

Treatment with candesartan cilexetil reduces mortality and hospitalisation due to CHF and improves symptoms as shown in the Candesartan in Heart failure - Assessment of Reduction in Mortality and

morbidity (CHARM) programme comprising three studies (CHARM-Alternative, CHARM-Added and CHARM-Preserved). In all three studies, patients on optimal baseline therapy 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.

### **CHARM-Alternative**

CHARM-Alternative was a multinational, randomised, double-blind placebo controlled study in CHF patients (NYHA class II-IV, n=2,028) with a LVEF  $\leq$ 40% not treated with an ACE inhibitor because of intolerance.

Effect of candesartan versus placebo on composite endpoints and their components in CHARM-Alternative

**Table 3**

<b>Endpoint</b>	<b>Absolute Risk Reduction (%)</b>	<b>Hazard Ratio (HR)</b>	<b>95% CI</b>	<b>Relative Risk Reduction (%)</b>
CV mortality or CHF hospitalisation	7.0	0.77	0.67-0.89, p<0.001	23
CV mortality	3.2	0.85	0.71-1.02, p=0.072	15
CHF hospitalisation	7.7	0.68	0.57-0.81, p<0.001	32
All-cause mortality or CHF hospitalisation	6.0	0.80	0.70-0.92, p=0.001	20
All-cause mortality	3.0	0.87	0.74-1.03, p=0.104	13

### **CHARM-Added**

CHARM-Added was a multinational, randomised, double-blind placebo controlled study in CHF patients (NYHA class II-IV, n=2,548) with a LVEF  $\leq$ 40% treated with ACE inhibitors.

Effect of candesartan versus placebo on composite endpoints and their components in CHARM-Added

**Table 4**

<b>Endpoint</b>	<b>Absolute Risk Reduction (%)</b>	<b>Hazard Ratio (HR)</b>	<b>95% CI</b>	<b>Relative Risk Reduction (%)</b>
CV mortality or CHF hospitalisation	4.4	0.85	0.75-0.96, p=0.011	15
CV mortality	3.6	0.84	0.72-0.98, p=0.029	16
CHF hospitalisation	3.8	0.83	0.71-0.96, p=0.013	17
All-cause mortality or CHF hospitalisation	3.9	0.87	0.78-0.98, p=0.021	13
All-cause mortality	2.8	0.89	0.77-1.02, p=0.086	11

### **CHARM-Preserved**

CHARM-Preserved was a multinational, randomised, double-blind placebo controlled study in CHF patients (n=3,023, NYHA class II-IV) with a LVEF > 40%, approximately 20% of whom received an ACE inhibitor. In the CHARM-Preserved study there was no effect of candesartan upon

mortality.

**Table 5**

<b>Endpoint</b>	<b>Absolute Risk Reduction (%)</b>	<b>Hazard Ratio (HR)</b>	<b>95% CI</b>	<b>Relative Risk Reduction (%)</b>
CV mortality or CHF hospitalisation	2.3	0.89	0.77-1.03, p=0.118	11
CV mortality	0.0	0.99	0.80-1.22, p=0.918	1
CHF hospitalisation	2.4	0.85	0.72-1.01, p=0.071	15
All-cause mortality or CHF hospitalisation	1.7	0.92	0.80-1.05, p=0.221	8
All-cause mortality	0.0	1.02	0.85-1.22, p=0.836	-

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). This corresponds to a relative risk reduction of 12% and 9% respectively and an absolute risk reduction of 2.9 and 1.6 respectively.

Treatment with candesartan cilexetil resulted in improved NYHA functional class in CHARM-Alternative and CHARM-Added (p=0.008 and p=0.020, respectively).

The beneficial effects of candesartan cilexetil on cardiovascular mortality and CHF hospitalisation were consistent irrespective of age, gender and concomitant medication. Candesartan cilexetil 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.

## **5.2 Pharmacokinetic properties**

### **Absorption and distribution**

Following oral administration, candesartan cilexetil is converted to the active drug 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 absolute bioavailability of candesartan following administration of the tablet is approximately 14%. The mean peak serum concentration ( $C_{max}$ ) is reached 3 to 4 hours following tablet intake. The candesartan serum concentrations increase linearly with increasing doses in the therapeutic dose range.

The area under the serum concentration versus time curve (AUC) of candesartan is not significantly affected by food. The peak concentration ( $C_{max}$ ) is increased by 26% and the rate of absorption is increased when taken with food. These changes are unlikely to result in clinically significant effects.

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

### **Biotransformation and elimination**

Candesartan is mainly eliminated unchanged via urine and bile and only eliminated by hepatic metabolism (CYP2C9) to a minor extent. 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 30% and 70% of the total radioactivity is recovered in the urine and faeces, respectively.

### **Pharmacokinetics in special populations**

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

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 (see section 4.2).

In patients with mild to moderate hepatic impairment, there was an increase in the AUC of candesartan of approximately 20%. In patients with moderate to severe hepatic impairment, the increase in the AUC of candesartan was approximately 80%. No initial dosage adjustment is necessary in these patients. There is only limited experience in patients with severe hepatic impairment and/or cholestasis (see section 4.2).

### **5.3 Preclinical safety data**

#### **Genotoxicity**

Candesartan showed no evidence of genotoxic potential in a series of assay for gene mutations (*Salmonella typhimurium*, *Escherichia coli*, Mouse L5178Y cells and CHO cells), chromosomal aberrations (mouse nucleus assay) and unscheduled DNA synthesis. The active metabolite, candesartan, caused an increase in chromosomal aberrations *in vitro* (CHL cells) but not *in vivo* (mouse micronucleus assay).

#### **Carcinogenicity**

There was no evidence of carcinogenicity when candesartan cilexetil was orally administered to mice and rats for up to 104 weeks at doses up to 100 and 1000 mg/kg/day, respectively. Rats received the drug by gavage whereas mice received the drug by dietary administration. These (maximally tolerated) doses of candesartan cilexetil provided systematic exposures to candesartan (AUCs) that were, in mice, approximately 7 times and, in rats, more than 70 times the exposure in man at the maximum recommended daily human dose (32 mg).

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## **6. Pharmaceutical Particulars**

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### **6.1 List of excipients**

Candesartan Viatrix tablets also contains:

- Lactose Monohydrate
- Maize Starch
- Hydroxypropylcellulose
- Carmellose Calcium
- Macrogol
- Magnesium Stearate
- Ferric Oxide Red

### **6.2 Incompatibilities**

Not applicable

### **6.3 Shelf life**

Blister packs: 24 months.

### **6.4 Special precautions for storage**

Store at or below 25°C.

### **6.5 Nature and contents of container**

Candesartan Viatris 4 mg tablet: Blister packs of 30 and 90 tablets

Candesartan Viatris 8 mg tablet: Blister packs of 30 and 90 tablets

Candesartan Viatris 16 mg tablet: Blister packs of 30 and 90 tablets

Candesartan Viatris 32 mg tablet: Blister packs of 30 and 90 tablets

Not all pack types and sizes may be marketed

### **6.6 Special precautions for disposal**

Not applicable.

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## **7. Medicines Schedule**

Prescription Medicine

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## **8. Sponsor Details**

Viatris Ltd  
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AUCKLAND  
[www.viatris.co.nz](http://www.viatris.co.nz)  
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## **9. Date of First Approval**

27 March 2026

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## **10. Date of Revision of the Text**

27 March 2026