

# Data Sheet

## Cardosart

### *Candesartan cilexetil 4 mg, 8 mg, 16 mg and 32 mg*

#### **PRESENTATION**

CARDOSART 4 mg are round (diameter 8 mm), biconvex, white to off-white tablets with a notch on one side and embossed on the same side.

CARDOSART 8 mg are round (diameter 8 mm), biconvex, white to off-white tablets with a notch on one side and embossed on the same side.

CARDOSART 16 mg are round (diameter 8 mm), biconvex, white to off-white tablets with a notch on one side and embossed on the same side.

CARDOSART 32 mg are round (diameter 10.5 mm), biconvex, white to off-white tablets with a notch on one side and embossed on the same side.

#### **USES**

#### **ACTIONS**

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.

CARDOSART 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 the degradation of bradykinin, angiotensin II receptor antagonists are unlikely to be associated with cough. In controlled clinical studies 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 (AT<sub>1</sub>) receptors results in dose related increases in plasma renin activity, angiotensin I and angiotensin II concentrations and a decrease in plasma aldosterone concentration.

### **Hypertension**

In hypertension, CARDOSART 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.

After administration of a single dose of CARDOSART onset of antihypertensive effect generally occurs within 2 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.

CARDOSART once daily provides effective and smooth blood pressure reduction over 24 hours, with little difference between maximum and trough effects during the dosing interval. In two 8-week randomised, double-blind studies, the blood pressure lowering effects of Candesartan cilexetil and losartan were evaluated in a total of 1,268 patients with mild to moderate hypertension. In both studies, the reduction of systolic and diastolic blood pressure was significantly greater with Candesartan cilexetil (32 mg once daily). In a pooled analysis, the trough blood pressure reduction (systolic/diastolic) was 13.1/10.5 mmHg with Candesartan cilexetil and 10.0/8.7 mmHg with losartan potassium (100 mg once daily). The mean difference in blood pressure reduction was 3.1/1.8 mmHg ( $p < 0.0001/p < 0.0001$ ).

CARDOSART can be used as monotherapy or in combination with other antihypertensive drugs, such as thiazide diuretics, dihydropyridine calcium antagonists and lisinopril, for enhanced efficacy.

CARDOSART is similarly effective in patients irrespective of age and gender. Candesartan cilexetil is effective in reducing blood pressure regardless of race, although the effect is somewhat less in black patients (usually a low-renin population). This is generally true for drugs that block the renin-angiotensin-aldosterone system.

Candesartan cilexetil increases renal blood flow and either has no effect on or increases glomerular filtration rate while renal vascular resistance and filtration fraction are reduced. Candesartan cilexetil also reduces urinary albumin excretion in patients with type II diabetes mellitus, hypertension and microalbuminuria. In hypertensive patients with type II diabetes mellitus, 12 weeks treatment with Candesartan cilexetil 8 mg to 16 mg had no adverse effects on blood glucose or lipid profile.

In the SCOPE (Study on Cognition and Prognosis in the Elderly) trial, the effects of candesartan cilexetil based antihypertensive treatment on cardiovascular morbidity and mortality, cognitive function and quality of life were assessed in 4,937 elderly patients (aged 70-89 years) with hypertension (SBP 160-179 mmHg and/or DBP 90-99 mmHg). The table shows the study results for the primary endpoint (major cardiovascular events) and its components. Both treatment regimens lowered systolic and diastolic blood pressure effectively and were generally well tolerated. Cognitive function and quality of life were well maintained in both treatment arms.

|                    | <b>Candesartan cilexetil*<br/>No. of pts with a first event<br/>(N=2477)</b> | <b>Control*<br/>No. of pts with a first event<br/>(N=2460)</b> | <b>Relative risk<br/>(95% CI)</b> | <b>P-value</b> |
|--------------------|--|--|-----------------------------------|----------------|
| Major CV events    | 242  | 268  | 0.89<br>(0.75-1.06)               | 0.19           |
| - CV mortality     | 145  | 152  | 0.95<br>(0.75-1.19)               | 0.63           |
| - Non-fatal stroke | 68   | 93   | 0.72<br>(0.53-0.99)               | 0.04           |
| - Non-fatal MI     | 54   | 47   | 1.14<br>(0.77-1.68)               | 0.52           |

\*Any previous antihypertensive treatment was standardized to hydrochlorothiazide 12.5 mg once daily before randomisation. Other antihypertensive treatment was added to the double-blind study medication (candesartan cilexetil 8-16 mg or corresponding placebo once daily) if SBP remained  $\geq 160$  mmHg and/or DBP  $\geq 90$  mmHg.

### **Heart Failure**

In patients with chronic heart failure (CHF) and depressed left ventricular systolic function (left ventricular ejection fraction, LVEF  $\leq 40\%$ ). 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. This multinational, placebo controlled, double-blind study programme in CHF patients with NYHA functional class II to IV consisted of three separate studies: CHARM-Alternative (n=2,028) in patients with LVEF  $\leq 40\%$  not treated with an ACE inhibitor because of intolerance, CHARM-Added (n=2,548) in patients with LVEF  $\leq 40\%$  and treated with an ACE inhibitor, and CHARM-Preserved (n=3,023) in patients with LVEF  $>40\%$ . Patients on optimal 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.

The composite endpoint of cardiovascular mortality or first CHF hospitalisation was significantly reduced with Candesartan cilexetil in comparison with placebo in CHARM-Alternative (hazard ratio (HR) 0.77, 95% CI 0.67-0.89,  $p < 0.001$ ) and in CHARM-Added (HR 0.85, 95% CI 0.75-0.96,  $p = 0.011$ ). This corresponds to a relative risk reduction of 23% and 15% respectively.

The composite endpoint of all-cause mortality or first CHF hospitalisation was also significantly reduced with Candesartan cilexetil in CHARM-Alternative (HR 0.80, 95% CI 0.70-0.92,  $p = 0.001$ ) and CHARM-Added (HR 0.87, 95% CI 0.78-0.98,  $p = 0.021$ ).

Both the mortality and morbidity (CHF hospitalisation) components of the composite endpoints contributed to the favourable effects of Candesartan cilexetil in CHARM-Alternative and CHARM-Added.

In CHARM-Preserved, no statistically significant reduction was achieved in the composite endpoint of cardiovascular mortality or first CHF hospitalisation.

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,  $p = 0.055$ ).

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.

## **PHARMACOKINETICS**

### **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 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.

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.

### **Metabolism and elimination**

Candesartan is mainly eliminated unchanged via urine and bile and only eliminated by hepatic metabolism (CYP2C9) to a minor extent. 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 <sup>14</sup>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) 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 DOSAGE AND ADMINISTRATION).

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%. There is only limited experience in patients with severe hepatic impairment and/or cholestasis (See DOSAGE AND ADMINISTRATION).

## INDICATIONS

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

## DOSAGE AND ADMINISTRATION

### Dosage in Hypertension

The recommended initial and maintenance dose of CARDOSART 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.

In patients with less than optimal blood pressure reduction on CARDOSART, 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  $\geq 30$  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

No initial dosage adjustment is necessary in patients with mild to moderate chronic liver disease. There is only limited experience available in patients with severe hepatic impairment and/or cholestasis. A lower initial dose of 4 mg should therefore be considered in these patients.

### Concomitant therapy

CARDOSART may be administered with other antihypertensive agents (see also "USES").

### Dosage in Heart Failure

The usual recommended initial dose for CARDOSART 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 WARNINGS AND PRECAUTIONS).

### **Special patient populations**

No initial dose adjustment is necessary for elderly patients or in patients with renal or hepatic impairment.

### **Concomitant therapy**

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

### **Administration**

CARDOSART should be taken once daily with or without food.

### **Use in children**

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

## **CONTRAINDICATIONS**

Hypersensitivity to any component of CARDOSART.

Pregnancy and lactation.

## **WARNINGS AND PRECAUTIONS**

### **Hypotension**

Hypotension may occur during treatment with CARDOSART 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.

### **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 CARDOSART.

When CARDOSART 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 mL/min/1.73 m<sup>2</sup> BSA).

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

### **Kidney transplantation**

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

### **Haemodialysis**

During dialysis the blood pressure may be particularly sensitive to AT<sub>1</sub>-receptor blockade as a result of reduced plasma volume and activation of the renin-angiotensin-aldosterone system. Therefore, CARDOSART should be carefully titrated with thorough monitoring of blood pressure in patients on haemodialysis. (See DOSAGE AND ADMINISTRATION).

### **Hepatic impairment**

There is only limited experience in patients with severe hepatic impairment and/or cholestasis.

### **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.

### **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) may lead to increases in serum potassium in hypertensive patients.

In heart failure patients treated with CARDOSART, hyperkalaemia may occur. During treatment with CARDOSART 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.

## **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 cardiopathy or ischaemic cerebrovascular disease could result in a myocardial infarction or stroke.

## ***USE IN PREGNANCY***

When used in pregnancy during the second and third trimesters, medicines that act directly on the renin-angiotensin system can cause foetal and neonatal injury and death. Animal studies with candesartan cilexetil have demonstrated late foetal and neonatal injury in the kidney. The mechanism is believed to be pharmacologically mediated through effects on the renin-angiotensin-aldosterone system.

In humans, foetal renal perfusion, which is dependent upon the development of the renin-angiotensin-aldosterone system, begins in the second trimester. Thus risk to the foetus increases if CARDOSART is administered during the second or third trimesters of pregnancy.

Based on the above information, CARDOSART should not be used in pregnancy. If pregnancy is detected during treatment, CARDOSART should be discontinued (see CONTRAINDICATIONS).

## ***USE IN LACTATION***

It is not known whether candesartan 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 CARDOSART is considered essential (see CONTRAINDICATIONS).

## ***EFFECTS ON ABILITY TO DRIVE AND USE MACHINES***

The effect of CARDOSART on the ability to drive and use machines has not been studied, but based on its pharmacodynamic properties CARDOSART 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.

## **ADVERSE 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%).

### **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. Increases in creatinine, urea or potassium and decreases in sodium have been observed. Increases in S-ALAT (S-GPT) were reported as adverse events slightly more often with Candesartan cilexetil than with placebo (1.3% vs. 0.5%). No routine monitoring of laboratory variables is necessary for patients receiving CARDOSART. However, in patients with severe renal impairment, periodic monitoring of serum potassium and creatinine levels should be considered.

### **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.

#### **Laboratory findings**

Increases in creatinine, urea and potassium. Periodic monitoring of serum creatinine and potassium is recommended (see WARNINGS AND PRECAUTIONS).

#### **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

**Skin and subcutaneous tissue disorders**

Angioedema, rash, urticaria, pruritus

**Musculoskeletal, connective tissue and bone disorders**

Back pain

**Renal and urinary disorders**

Renal impairment, including renal failure in susceptible patients (see WARNINGS AND PRECAUTIONS).

Although causality to candesartan has not been established, palpitation has been very rarely reported as an adverse event during post-marketing surveillance

**INTERACTIONS**

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

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 and careful monitoring of serum lithium levels is recommended during concomitant use.

The antihypertensive effect of CARDOSART may be enhanced by other antihypertensives.

The bioavailability of candesartan is not affected by food.

**OVERDOSAGE****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 is not removed by haemodialysis.

## **PHARMACEUTICAL PRECAUTIONS**

### **List of excipients**

Maize starch, Lactose monohydrate, Triethyl citrate, Hydroxypropylcellulose, Croscarmellose sodium, Magnesium stearate.

### **Incompatibilities**

Nil

### **Shelf-life**

36 months in PVC/PVDC-Al blisters

### **Special precautions for storage**

Store below 25 °C.

## **MEDICINES CLASSIFICATION**

Prescription Medicine

## **PACKAGE QUANTITIES**

4 mg tablet: Blister packs of 28 or 30 tablets

8 mg tablet: Blister packs of 28 or 30 tablets

16 mg tablet: Blister packs of 28 or 30 tablets

32 mg tablet: Blister packs of 28 or 30 tablets

## **FURTHER INFORMATION**

### ***PRECLINICAL SAFETY DATA***

In a variety of preclinical safety studies conducted in several species, expected exaggerated pharmacological effects, 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. Foetotoxicity has been observed in late pregnancy (see sections regarding Pregnancy and Lactation).

There was no evidence of mutagenicity, clastogenicity or carcinogenicity.

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**DATE OF PREPARATION**

May 2010