Core Safety Profile

Active substance: Candesartan
Pharmaceutical form(s)/strength: 2, 4, 8, 16 and 32mg Tablets
P-RMS: UK/H/PSUR/0036/001
Date of FAR: 12.07.2010
4.2 Posology and method of administration

**Dosage in hypertension**

The recommended initial dose and usual maintenance dose is 8 mg once daily. The dose may be increased to 16 mg once daily. If blood pressure is not sufficiently controlled after 4 weeks of treatment with 16 mg once daily, the dose may be further increased to a maximum of 32 mg once daily (see section 5.1 Pharmacodynamic properties). If blood pressure control is not achieved with this dose, alternative strategies should be considered.

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

**Use in the elderly**

No initial dosage adjustment is necessary in elderly patients.

**Use in 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 also 4.4 Special warnings and special precautions for use).

**Use in impaired renal function**

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 special warnings and special precautions for use.

**Use in impaired hepatic function**

An initial dose of 2 mg once daily is recommended in patients with mild to moderate hepatic impairment. The dose may be adjusted according to response. There is no experience in patients with severe hepatic impairment.

**Concomitant therapy**

Addition of a thiazide-type diuretic such as hydrochlorothiazide has been shown to have an additive antihypertensive effect with <product name>.

**Dosage in heart failure**

The usual recommended initial dose of <product name> 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 Special warnings and special precautions for use).

**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.

**Concomitant therapy**

<Product name> can be administered with other heart failure treatment, including ACE inhibitors, beta-blockers, diuretics and digitalis or a combination of these medicinal products (see also section 4.4 Special warnings and special precautions for use and 5.1 Pharmacodynamic properties).
Administration

<Product name> should be taken once daily with or without food.

Use in black patients

The antihypertensive effect of candesartan is less in black than non-black patients. Consequently, up titration of <product name> and concomitant therapy may be more frequently needed for blood pressure control in black than non-black patients (see section 5.1 Pharmacodynamic properties).

Use in children and adolescents

The safety and efficacy of <product name> have not been established in children and adolescents (under 18 years).

4.3 Contraindications

Hypersensitivity to candesartan cilexetil or to any of the excipients.

Pregnancy and lactation (see section 4.6 Pregnancy and lactation).

Severe hepatic impairment and/or cholestasis.

4.4 Special warnings and precautions for use

Renal impairment

As with other agents inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible patients treated with <product name>.

When <product name> 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 (Clcreatine < 15 ml/min). In these patients <product name> 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 <product name>, 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 renal function impairment and hyperkalaemia, may increase when candesartan is used in combination with an ACE inhibitor (see section 4.8 Undesirable effects). Patients with such treatment should be monitored regularly and carefully.
Haemodialysis

During dialysis the blood pressure may be particularly sensitive to AT₁-receptor blockade as a result of reduced plasma volume and activation of the renin-angiotensin-aldosterone system. Therefore <product name> should be carefully titrated with thorough monitoring of blood pressure in patients on haemodialysis.

Renal artery stenosis

Other medicinal products 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.

Kidney transplantation

There is no experience regarding the administration of <product name> in patients with a recent kidney transplantation.

Hypotension

Hypotension may occur during treatment with <product name> 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 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 <product name> is not recommended.
**Hyperkalaemia**

Based on experience with the use of other medicinal products that affect the renin-angiotensin-aldosterone system, concomitant use of `<product name>` 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.

In heart failure patients treated with `<product name>`, hyperkalaemia may occur. During treatment with `<product name>` 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.

**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 angiotensin II receptor antagonists. 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.

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**

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.

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 isoenzymes is presently unknown.

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.

Based on experience with the use of other medicinal products that affect the renin-angiotensin-aldosterone system, concomitant use of 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.

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.
When Angiotensin II receptor antagonists are administered simultaneously with non-steroidal anti-inflammatory drugs (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 Angiotensin II receptor antagonists 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.

The bioavailability of candesartan is not affected by food.

4.6 Pregnancy and lactation

Use in pregnancy

There are very limited data from the use of <product name> in pregnant women. These data are insufficient to allow conclusions about potential risk for the foetus when used during the first trimester. 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 <product name> is administered during the second or third trimesters of pregnancy. When used in pregnancy during the second and third trimesters, medicinal products that act directly on the renin-angiotensin system can cause foetal and neonatal injury (hypotension, renal dysfunction, oliguria and/or anuria, oligohydramnios, skull hypoplasia, intrauterine growth retardation) and death. Cases of lung hypoplasia, facial abnormalities and limb contractures have also been described.

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.

Based on the above information, <product name> should not be used in pregnancy. If pregnancy is detected during treatment, <product name> should be discontinued (see section 4.3 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, <product name> should not be given during breast-feeding (see section 4.3 Contraindications).

4.7 Effects on ability to drive and use machines

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

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

In a pooled analysis of clinical trial data, the following adverse reactions with candesartan cilexetil were reported based on an incidence of adverse events with candesartan cilexetil at least 1% higher than the incidence seen with placebo:

The frequencies used in the tables throughout this section are: very common (≥ 1/10), common (≥ 1/100 <1/10), uncommon (≥ 1/1000, <1/100), rare (≥ 1/10 000, <1/1000) and very rare (<1/10 000)

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Frequency</th>
<th>Undesirable Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td>Common</td>
<td>Respiratory infection</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Common</td>
<td>Dizziness/vertigo, headache</td>
</tr>
</tbody>
</table>

**Laboratory findings**

In general, there were no clinically important influences of <product name> 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 decrease in sodium have been observed. Increases in S-ALAT (S-GPT) were reported as adverse events slightly more often with <product name> than with placebo (1.3% vs 0.5%). No routine monitoring of laboratory variables is usually necessary for patients receiving <product name>. 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 <product name> 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 <product name> 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 seen were:

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Frequency</th>
<th>Undesirable Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Common</td>
<td>Hyperkalaemia</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Common</td>
<td>Hypotension</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Common</td>
<td>Renal impairment</td>
</tr>
</tbody>
</table>

**Laboratory findings**

Increases in creatinine, urea and potassium. Periodic monitoring of serum creatinine and potassium is recommended (see section 4.4 Special warnings and special precautions for use).
Post marketing

The following adverse reactions have been reported in post marketing experience:

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

4.9 Overdose

Symptoms

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

Management

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

Candesartan is not removed by haemodialysis.