PRODUCT INFORMATION
CANDESARTAN SANDOZ® 4 MG, 8 MG, 16 MG, 32 MG TABLETS

NAME OF THE MEDICINE

Candesartan cilexetil

(+/-)-1-(cyclohexyloxycarbonyl-oxy) ethyl 2-ethoxy- 1-[[2'-(1H-tetrazol- 5-yl)biphenyl- 4-yl] methyl]- 1H-benzimadozole- 7-carboxylate

CAS [145040-37-5]
Empirical formula: C_{33}H_{34}N_{6}O_{6} MW: 610.7

DESCRIPTION

Candesartan cilexetil is a white to off white powder and is practically insoluble in water. Three polymorphic forms have been identified; crystal form I, crystal form II and an amorphous form. Crystalline form I is used in Candesartan Sandoz.

Excipients: Lactose monohydrate, iron oxide red (8mg, 16mg and 32mg tablets only), titanium dioxide (8mg, 16mg and 32mg tablets only), maize starch, povidone, carrageenan, croscarmellose sodium, magnesium stearate.

PHARMACOLOGY

Pharmacodynamics
Candesartan cilexetil is a Angiotensin II receptor antagonist.
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, e.g. vasoconstriction, aldosterone stimulation, regulation of salt and...
water homeostasis and stimulation of cell growth, are mediated via the type 1 (AT\textsubscript{1}) 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\textsubscript{1} receptors, with tight binding to and slow dissociation from the receptor. It has no agonist activity.

Candesartan does not inhibit angiotensin converting enzyme (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 cilexetil 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 pressure reduction over the 24 hour dosing interval, with a trough/peak ratio confirming once daily dosing.

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

Candesartan cilexetil 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 cilexetil reduces urinary protein excretion in hypertensive patients with microalbuminuria or nephropathy of different aetiology. Candesartan cilexetil 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. Foetotoxicity has been observed in late pregnancy (see PRECAUTIONS, Use in Pregnancy and Use in Lactation).

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 little variability. The absolute bioavailability of candesartan following administration of the tablet is approximately 14%. The mean peak serum concentration (C_{max}) is reached three to four hours after taking a tablet. The point estimate of C_{max} is 103.83% with associated confidence interval of [96.65%, 111.55%]. 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.

In case of AUC_{0-t}, the point estimate is 95.45% with associated confidence interval of [91.14%, 99.96%] and AUC_{0-\infty} has point estimate of 94.96% and corresponding associated confidence interval of [90.73%, 99.37%].

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

Metabolism and elimination
Candesartan is mainly eliminated unchanged via urine and bile and is eliminated by hepatic metabolism only to a minor extent. The terminal half-life of candesartan is approximately nine hours. There is no accumulation following multiple doses. Total plasma clearance of candesartan is about 0.37 mL/minute/kg, with a renal clearance of about 0.19 mL/minute/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 about 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 in comparison to young subjects. An initial dose of 8 mg is recommended (see DOSAGE AND ADMINISTRATION).

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. AUC of candesartan in patients undergoing haemodialysis was similar to that in patients with severe renal impairment.
In patients with mild to moderate hepatic impairment, there was a 23% increase in the AUC of candesartan. No initial dosage adjustment is necessary in these patients.

Following oral administration of Candesartan Sandoz 16mg to healthy subjects under fasting conditions, a mean peak plasma concentration ($C_{\text{max}}$) of candesartan of approximately 118.18ng/mL was achieved within approximately 4.02 hours ($T_{\text{max}}$).

**CLINICAL TRIALS**

**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 2 diabetes mellitus, hypertension and microalbuminuria. Patients were randomly allocated to four treatment regimens: 1) 24 weeks of candesartan monotherapy (one-third of the patients); 2) 24 weeks of lisinopril monotherapy (one-third of the patients); 3) 12 weeks of candesartan monotherapy, followed by 12 weeks of candesartan + lisinopril combination therapy (one-sixth of the patients); and 4) 12 weeks of lisinopril monotherapy, followed by 12 weeks of lisinopril and candesartan combination therapy (one-sixth 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, one-third of the patients still in the study were on candesartan monotherapy (n = 49), one-third on lisinopril monotherapy (n = 46), and one-third on combination therapy (candesartan and lisinopril (n = 25); lisinopril and candesartan (n = 24). (See Table 1.)

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 1.)

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Baseline</th>
<th>Change at 12 weeks</th>
<th>Change at 24 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SBP mmHg</td>
<td>DBP mmHg</td>
<td>SBP mmHg</td>
</tr>
<tr>
<td>Candesartan 16 mg (n=49)</td>
<td>162</td>
<td>96</td>
<td>-15</td>
</tr>
<tr>
<td>Lisinopril 20 mg (n=46)</td>
<td>161</td>
<td>96</td>
<td>-14</td>
</tr>
<tr>
<td>Candesartan 16 mg + Lisinopril 20 mg from 12 weeks (n=25)</td>
<td>161</td>
<td>95</td>
<td>-16</td>
</tr>
</tbody>
</table>
Lisinopril 20 mg + Candesartan 16 mg from 12 weeks (n=24)

<table>
<thead>
<tr>
<th>Absolute Risk Reduction (%)</th>
<th>Hazard Ratio (HR)</th>
<th>95% CI</th>
<th>Relative Risk Reduction (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV mortality or CHF</td>
<td>7.0</td>
<td>0.77</td>
<td>0.67-0.89, p&lt;0.001</td>
</tr>
<tr>
<td>hospitalisation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CV mortality</td>
<td>3.2</td>
<td>0.85</td>
<td>0.71-1.02, p=0.072</td>
</tr>
<tr>
<td>CHF hospitalisation</td>
<td>7.7</td>
<td>0.68</td>
<td>0.57-0.81, p&lt;0.001</td>
</tr>
<tr>
<td>All-cause mortality or CHF</td>
<td>6.0</td>
<td>0.80</td>
<td>0.70-0.92, p=0.001</td>
</tr>
<tr>
<td>hospitalisation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>3.0</td>
<td>0.87</td>
<td>0.74-1.03, p=0.104</td>
</tr>
</tbody>
</table>

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

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 less than or equal to 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) program 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 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 (New York Heart Association (NHYA) class II to IV, n = 2,028) with a LVEF less than or equal to 40% not treated with an ACE inhibitor because of intolerance. See Table 2.

**Table 2: Effect of candesartan versus placebo on composite endpoints and their components in CHARM-Alternative.**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Absolute Risk Reduction (%)</th>
<th>Hazard Ratio (HR)</th>
<th>95% CI</th>
<th>Relative Risk Reduction (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV mortality or CHF hospitalisation</td>
<td>7.0</td>
<td>0.77</td>
<td>0.67-0.89, p&lt;0.001</td>
<td>23</td>
</tr>
<tr>
<td>CV mortality</td>
<td>3.2</td>
<td>0.85</td>
<td>0.71-1.02, p=0.072</td>
<td>15</td>
</tr>
<tr>
<td>CHF hospitalisation</td>
<td>7.7</td>
<td>0.68</td>
<td>0.57-0.81, p&lt;0.001</td>
<td>32</td>
</tr>
<tr>
<td>All-cause mortality or CHF hospitalisation</td>
<td>6.0</td>
<td>0.80</td>
<td>0.70-0.92, p=0.001</td>
<td>20</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>3.0</td>
<td>0.87</td>
<td>0.74-1.03, p=0.104</td>
<td>13</td>
</tr>
</tbody>
</table>
CHARM-Added. CHARM-Added was a multinational, randomised, double blind placebo controlled study in CHF patients (NYHA class II to IV, n = 2,548) with a LVEF less than or equal to 40% treated with ACE inhibitors. See Table 3.

Table 3: Effect of candesartan versus placebo on composite endpoints and their components in CHARM-Added.

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

CHARM-Preserved. CHARM-Preserved was a multinational, randomised, double blind placebo controlled study in CHF patients (n = 3,023, NYHA class II to 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. See Table 4.

Table 4: Effect of candesartan versus placebo on composite endpoints and their components in CHARM-Added.

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Absolute Risk Reduction (%)</th>
<th>Hazard Ratio (HR)</th>
<th>95% CI</th>
<th>Relative Risk Reduction (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV mortality or CHF hospitalisation</td>
<td>2.3</td>
<td>0.89</td>
<td>0.77-1.03, p=0.018</td>
<td>11</td>
</tr>
<tr>
<td>CV mortality</td>
<td>0.0</td>
<td>0.99</td>
<td>0.80-1.22, p=0.918</td>
<td>1</td>
</tr>
<tr>
<td>CHF hospitalisation</td>
<td>2.4</td>
<td>0.85</td>
<td>0.72-1.01, p=0.071</td>
<td>15</td>
</tr>
<tr>
<td>All-cause mortality or CHF hospitalisation</td>
<td>1.7</td>
<td>0.92</td>
<td>0.80-1.05, p=0.021</td>
<td>8</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>0.0</td>
<td>1.02</td>
<td>0.85-1.22, p=0.836</td>
<td>-</td>
</tr>
</tbody>
</table>

All-cause mortality was also assessed in pooled populations, CHARM-Alternative and CHARM-Added (HR 0.88, 95% CI: 0.79 to 0.98, p = 0.018) and all three studies (HR 0.91, 95% CI: 0.83 to 1.00, p = 0.055). 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 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.

**INDICATIONS**

- Treatment of hypertension.
- Treatment of patients with heart failure and impaired left ventricular systolic function (left ventricular ejection fraction less than or equal to 40%) as add on therapy to ACE inhibitors or when ACE inhibitors are not tolerated.

**CONTRAINdications**

- History of previous hypersensitivity to the active ingredient candesartan cilexetil or to any excipient ingredients present in Candesartan Sandoz.
- Pregnancy and lactation (see PRECAUTIONS, Use in pregnancy).
- Severe hepatic impairment and/or cholestasis
- The use of Candesartan Sandoz in combination aliskiren-containing medicines in patients with diabetes mellitus (type I or II) or with moderate to severe renal impairment (GFR<60mL/min/1.73m²).

**PRECAUTIONS**

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 medicines 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.

*Kidney transplantation*

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

*Renal artery stenosis*

Other medicines 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.

*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 medicines acting through inhibition of the renin angiotensin aldosterone system. Therefore, the use of candesartan in these patients is not recommended.

**Hypotension**

Hypotension may occur during treatment with candesartan 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) with aliskiren-containing medicines**

Dual blockade of the renin-angiotensin-aldosterone system by combining candesartan cilexetil and aliskiren is not recommended since there is an increased risk of hypotension, hyperkalaemia and changes in renal function. The use of Candesartan Sandoz with aliskiren is contraindicated in patients with diabetes mellitus (type I or II) or moderate to severe renal impairment (GFR<60ml/min/1.73m2) (see CONTRAINDICATIONS).

**Hyperkalaemia**

Based on experience with the use of other medicines that affect the renin angiotensin aldosterone system, concomitant use of candesartan cilexetil with potassium sparing diuretics, potassium supplements, salt substitutes containing potassium, or other medicines that may increase potassium levels (e.g. heparin) may lead to increases in serum potassium in hypertensive patients. Monitoring of potassium should be undertaken as appropriate.

In heart failure patients treated with candesartan, hyperkalaemia may occur. During treatment with candesartan in patients with heart failure, periodic monitoring of serum potassium is recommended. The combination of an ACE inhibitor, a potassium-sparing diuretic, such as spironolactone, and candesartan cilexetil is not recommended and should be considered only after careful evaluation of the potential benefits and risks.

**Haemodialysis**

During dialysis the blood pressure may be particularly sensitive to AT1-receptor blockade as a result of reduced plasma volume and activation of the renin angiotensin aldosterone system. Therefore, candesartan should be carefully titrated with thorough monitoring of blood pressure in patients on haemodialysis (see DOSAGE AND ADMINISTRATION).

**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.

Combination use of angiotensin converting enzyme inhibitors or angiotensin receptor antagonists, anti-inflammatory drugs and thiazide diuretics

The use of an ACE inhibiting medicine (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 medicine. Combined use of these medications should be accompanied by increased monitoring of serum creatinine, particularly at the institution of the combination. The combination of medicines from these three classes should be used with caution particularly in elderly patients or those with pre-existing renal impairment.

Impaired renal function

As with other agents inhibiting the renin angiotensin aldosterone system (RAAS), changes in renal function may be anticipated in susceptible patients treated with candesartan. When candesartan 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 endstage renal impairment (i.e. creatinine clearance < 15 mL/minute/1.73 m² BSA). Evaluation of patients with heart failure should include periodic assessments of renal function. During dose titration of candesartan, monitoring of serum creatinine and potassium is recommended.

Impaired hepatic function

There is no experience in patients with severe hepatic impairment and/or cholestasis; caution is advised in these patients. 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.

Effects on 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.

Use in pregnancy. (Category D)

Medicines that act on the renin angiotensin system (RAS) can cause foetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature in patients who were taking angiotensin converting enzyme inhibitors. When pregnancy is detected, candesartan should be discontinued as soon as possible.

The use of medicines that act directly on the renin angiotensin system during the second and third trimesters of pregnancy have been associated with foetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydraminos has been reported, presumably resulting from decreased foetal renal function; oligohydraminos in this setting has been associated with foetal limb contractures, craniofacial deformation and
hypoplastic lung development. Prematurity, intrauterine growth retardation and patent
ductus arteriosus have also been reported, although it is not clear whether these
occurrences were due to exposure to the medicine.

In addition, in retrospective data, first trimester use of ACE inhibitors has been
associated with a potential risk of birth defects. There have been reports of
spontaneous abortion, oligohydramnios and newborn renal dysfunction, when
pregnant women have inadvertently taken the angiotensin II antagonist valsartan. As
for any drug that also acts directly on the RAAS, candesartan cilexetil should not be
used during pregnancy (see CONTRAINDICATIONS) or in women planning to
become pregnant. Healthcare professionals prescribing any agents acting on the
RAAS should counsel women of childbearing potential about the potential risk of
these agents during pregnancy. If pregnancy is detected during therapy, candesartan
cilexetil should be discontinued as soon as possible.

Infants with histories of in utero exposure to an angiotensin II receptor antagonist
should be closely observed for hypotension, oliguria and hyperkalaemia.

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 breastfed infant, breastfeeding should be discontinued if the use of candesartan is
considered essential.

Paediatric use
The safety and efficacy of candesartan cilexetil have not been established in children.

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 1,000
mg/kg/day, respectively. Rats received the medicine by gavages whereas mice
received the medicine by dietary administration. These (maximally tolerated) doses of
candesartan cilexetil provided systematic exposures to candesartan (AUCs) that were,
in mice, approximately seven times and, in rats, more than 70 times the exposure in
humans at the maximum recommended daily human dose (32 mg).

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).

Effect on ability to drive or operate machinery
When driving vehicles or operating machines, it should be taken into account that
dizziness or weariness may occur during treatment.
INTERACTIONS WITH OTHER MEDICINES

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<60ml/min/1.7m²) 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 blocker 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 Contraindications and Precautions).

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

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

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

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

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 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 isoenzymes is presently unknown.

Candesartan may be administered with other antihypertensive agents.
ADVERSE EFFECTS

Hypertension
Candesartan cilexetil was well tolerated in clinical studies showing an adverse event profile comparable to that of placebo. Generally adverse events were mild and transient. The overall incidence of adverse effects 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 cilexetil was administered as monotherapy 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 in Table 5.

Table 5

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Monotherapy Studies</th>
<th>Combination Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Candesartan cilexetil</td>
</tr>
<tr>
<td></td>
<td>(n=573)</td>
<td>(n=1388)</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>peripheral oedema</td>
<td>0.7%</td>
<td>1.3%</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>nausea</td>
<td>1.4%</td>
<td>2.2%</td>
</tr>
<tr>
<td>abdominal pain</td>
<td>1.9%</td>
<td>1.7%</td>
</tr>
<tr>
<td>diarrhoea</td>
<td>2.3%</td>
<td>1.6%</td>
</tr>
<tr>
<td>vomiting</td>
<td>1.0%</td>
<td>1.2%</td>
</tr>
<tr>
<td>Musculo-skeletal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>back pain</td>
<td>1.2%</td>
<td>4.0%</td>
</tr>
<tr>
<td>Nervous system</td>
<td></td>
<td></td>
</tr>
<tr>
<td>headache</td>
<td>10.7%</td>
<td>10.9%</td>
</tr>
<tr>
<td>dizziness</td>
<td>2.6%</td>
<td>2.7%</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
</tr>
<tr>
<td>influenza-like symptoms</td>
<td>1.0%</td>
<td>1.9%</td>
</tr>
<tr>
<td>inflicted injury</td>
<td>0.9%</td>
<td>1.7%</td>
</tr>
<tr>
<td>fatigue</td>
<td>1.6%</td>
<td>1.5%</td>
</tr>
<tr>
<td>Respiratory</td>
<td></td>
<td></td>
</tr>
<tr>
<td>URTI</td>
<td>3.9%</td>
<td>6.1%</td>
</tr>
<tr>
<td>bronchitis</td>
<td>2.6%</td>
<td>1.9%</td>
</tr>
<tr>
<td>coughing</td>
<td>1.8%</td>
<td>1.9%</td>
</tr>
<tr>
<td>pharyngitis</td>
<td>0.7%</td>
<td>1.9%</td>
</tr>
<tr>
<td>rhinitis</td>
<td>0.5%</td>
<td>1.3%</td>
</tr>
<tr>
<td>HCTZ = hydrochlorothiazide</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Median (mean) duration of exposure: placebo: 57 (68 days) and candesartan cilexetil: 56 (78) days.
Laboratory findings
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. Increases in creatinine, urea or potassium and decreases in sodium have been observed. In clinical trials, elevations of alanine aminotransferase (ALT) occurred in 1.3% of candesartan treated patients and 0.5% of those treated with placebo. The incidence of aspartate aminotransferase (AST) elevation was 0.4% with candesartan and 0% with placebo. No routine monitoring of laboratory variables is usually 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
The adverse experience profile of candesartan cilexetil in heart failure patients was consistent with the pharmacology of the medicine and the health status of the patients. In the CHARM clinical program, 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 (greater than or equal to 1/100, < 1/10) seen were as follows:

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 PRECAUTIONS).

Postmarketing
The following adverse reactions have been reported very rarely (< 0.01%) in postmarketing experience.

Blood and lymphatic system disorders
Leucopenia, neutropenia and agranulocytosis

Metabolism and nutrition disorders
Hyperkalaemia, hyponatraemia

Hepatobiliary 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, myalgia

Renal and urinary disorders
Renal impairment, including renal failure in susceptible patients (see PRECAUTIONS, Renal impairment).

Respiratory, thoracic and mediastinal disorders
Very rare: cough

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

Although causality to candesartan has not been established, the following neuropsychiatric and cardiovascular adverse reactions have been very rarely reported during postmarketing surveillance. These were agitation, anxiety, depression, insomnia, somnolence, nervousness, nightmare, sleep disorder and palpitations.

DOSAGE AND ADMINISTRATION

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

Hypertension
The recommended maintenance dose of Candesartan Sandoz is 8 or 16 mg once daily. The maximal antihypertensive effect is attained within four weeks following initiation of treatment. For those patients who start on 8 mg and require further blood pressure reduction, a dose increase to 16 mg is recommended. An initial dose of 16 mg is also well tolerated. Some patients may receive an additional benefit by increasing the dose to 32 mg once daily.

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

Use in the elderly
An initial dose of 8 mg is recommended.

Hepatic insufficiency
No initial dosage adjustment is necessary in patients with mild to moderately chronic liver disease. No experience is available to date in patients with severely impaired hepatic function (e.g. cirrhotic patients).

Renal insufficiency
No initial dosage adjustment is necessary in patients with mild to moderate impaired renal function (i.e. creatinine clearance greater than or equal to 30 mL/minute/1.73 m² body surface area (BSA)). In patients with severely impaired renal function (i.e. creatinine clearance < 30 mL/minute/1.73 m² BSA), including patients on haemodialysis, a lower initial dose of 4 mg should be considered.
Heart failure
The usual recommended initial dose of Candesartan Sandoz is 4 mg once daily. Up titration to the target dose of 32 mg once daily or the highest tolerated dose is performed by doubling the dose at intervals of at least two weeks (see PRECAUTIONS).

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

Concomitant therapy
Candesartan Sandoz can be administered with other heart failure treatment, including ACE inhibitors, beta-blockers, diuretics and digitalis or a combination of these medicines (see also PHARMACOLOGY).

OVERDOSAGE
Contact the Poisons Information Centre on 13 11 26 for advice on management of 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 candesartan cilexetil 672 mg) patient recovery was uneventful.

Treatment
If symptomatic hypotension should occur, symptomatic treatment should be instituted and vital signs monitored. The patients should be placed supine with the legs elevated. If this is not sufficient, plasma volume should be increased by the infusion of, e.g., isotonic saline solution. Sympathomimetic medicines may be administered if the abovementioned measures are not sufficient.

Candesartan is not removed by haemodialysis.

PRESENTATION AND STORAGE CONDITIONS
Candesartan Sandoz 4mg tablets – White, round biconvex tablet, debossed with 4 on one side and scored on the other.
Candesartan Sandoz 8mg tablets – Pink, mottled, round biconvex tablet, debossed with 8 on one side and scored on the other.
Candesartan Sandoz 16mg tablets – Pink, mottled, round biconvex tablet, debossed with 16 on one side and scored on the other.
Candesartan Sandoz 32mg tablets – Pink, mottled, round biconvex tablet, debossed with 32 on one side and scored on the other.

Candesartan Sandoz is available in blister packs of 30 tablets.
Store below 30 °C. Store in the original packaging.
NAME AND ADDRESS OF THE SPONSOR

Sandoz Pty Ltd
ABN 60 075 449 553
54 Waterloo Road
Macquarie Park NSW 2113
Australia
Tel: 1800 634 500

POISON SCHEDULE OF THE MEDICINE

Schedule 4 – Prescription Only Medicine

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (the ARTG): 5/01/2011

DATE OF MOST RECENT AMENDMENT: 28 November 2016