Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Candesartan Hydrochlorothiazide 16 mg/12.5 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One Candesartan Hydrochlorothiazide 16 mg/12.5 mg tablet contains 16 mg candesartan cilexetil and 12.5 mg hydrochlorothiazide.

Excipients with known effect:

Each tablet contains 109.30 mg lactose monohydrate.

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablet.
Candesartan Hydrochlorotiazide 16 mg/12.5 mg Tablets are white, round, biconvex tablets with a score line on one side and an embossing CH16 on the same side.

The tablet can be divided into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Candesartan Hydrochlorothiazide is indicated for the:

- Treatment of primary hypertension in adult patients whose blood pressure is not optimally controlled with candesartan cilexetil or hydrochlorothiazide monotherapy.

4.2 Posology and method of administration

Posology
The recommended dose of Candesartan Hydrochlorothiazide is one tablet once daily.

Dose titration with the individual components (candesartan cilexetil and hydrochlorothiazide) is recommended. When clinically appropriate a direct change from monotherapy to Candesartan Hydrochlorothiazide may be considered. Dose titration of candesartan cilexetil is recommended when switching from hydrochlorothiazide monotherapy.

Candesartan Hydrochlorothiazide may be administered in patients whose blood pressure is not optimally controlled with candesartan cilexetil or hydrochlorothiazide monotherapy or Candesartan Hydrochlorothiazide at lower doses (see sections 4.3, 4.4, 4.5 and 5.1).

Most of the antihypertensive effect is usually attained within 4 weeks of initiation of treatment.

Special populations
Elderly population
No dose adjustment is necessary in elderly patients.

Patients with intravascular volume depletion
Dose titration of candesartan cilexetil is recommended in patients at risk for hypotension, such as patients with possible volume depletion (an initial dose of candesartan cilexetil of 4 mg may be considered in these patients).

Patients with renal impairment

In patients with mild to moderate renal impairment (creatinine clearance 30-80 ml/min/1.73m^2 BSA) a dose titration is recommended.

Candesartan Hydrochlorothiazide is contraindicated in patients with severe renal impairment (creatinine clearance <30 ml/min/1.73 m^2 BSA) (see section 4.3).

Patients with hepatic impairment
Dose titration of candesartan cilexetil is recommended in patients with mild to moderate hepatic impairment.

Candesartan Hydrochlorothiazide is contraindicated in patients with severe hepatic impairment and/or cholestasis (see section 4.3).

Paediatric population
The safety and efficacy of Candesartan Hydrochlorothiazide in children aged between birth and 18 years have not been established. No data are available.

Method of administration
Oral use.
Candesartan Hydrochlorothiazide can be taken with or without food.
The bioavailability of candesartan is not affected by food.
There is no clinically significant interaction between hydrochlorothiazide and food.

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1 or to sulfonamide derived active substances. Hydrochlorothiazide is a sulfonamide derived active substance.
- Second and third trimesters of pregnancy (see sections 4.4 and 4.6).
- Severe renal impairment (creatinine clearance <30 ml/min/1.73 m^2 BSA).
- Severe hepatic impairment and/or cholestasis.
- Refractory hypokalaemia and hypercalcaemia.
- Gout.
- The concomitant use of Candesartan Hydrochlorotiazide with aliskiren containing product is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m^2) (see sections 4.5 and 5.1).

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 Candesartan Hydrochlorothiazide (see section 4.3).

Kidney transplantation
There is limited clinical evidence regarding Candesartan Hydrochlorothiazide use in patients who have undergone renal transplant.

Renal artery stenosis
Medicinal products that affect the renin-angiotensin-aldosterone system, including angiotensin II receptor antagonists (AIIRAs), may increase blood urea and serum creatinine in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney.

Intravascular volume depletion
In patients with intravascular volume and/or sodium depletion symptomatic hypotension may occur, as described for other agents acting on the renin-angiotensin-aldosterone system. Therefore, the use of Candesartan Hydrochlorothiazide tablets is not recommended until this condition has been corrected.

Anaesthesia and surgery
Hypotension may occur during anaesthesia and surgery in patients treated with AIIRAs 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.

Hepatic impairment
Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma. There is no clinical experience with Candesartan Hydrochlorothiazide tablets in patients with hepatic impairment.

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 generally will not respond to antihypertensive agents acting through inhibition of the renin-angiotensin-aldosterone system. Therefore the use of Candesartan Hydrochlorothiazide tablets is not recommended in this population.

Electrolyte imbalance
Periodic determination of serum electrolytes should be performed at appropriate intervals. Thiazides, including hydrochlorothiazide, can cause fluid or electrolyte imbalance (hypercalcaemia, hypokalaemia, hyponatraemia, hypomagnesaemia and hypochloraemic alkalosis).

Thiazide diuretics may decrease the urinary calcium excretion and may cause intermittent and slightly increased serum calcium concentrations. Marked hypercalcaemia may be a sign of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Hydrochlorothiazide dose-dependently increases urinary potassium excretion which may result in hypokalaemia. This effect of hydrochlorothiazide seems to be less evident when combined with candesartan cilexetil. The risk for hypokalaemia may be increased in patients with cirrhosis of the liver, in patients experiencing brisk diuresis, in patients with an inadequate oral intake of electrolytes and in patients receiving concomitant therapy with corticosteroids or adrenocorticotropic hormone (ACTH).

Treatment with candesartan cilexetil may cause hyperkalaemia, especially in the presence of heart failure and/or renal impairment. Concomitant use of Candesartan Hydrochlorothiazide and ACE inhibitors, aliskiren, and potassium-sparing diuretics, potassium supplements or salt substitutes or other medicinal products that may increase serum potassium levels (e.g. heparin sodium, co-trimoxazole also known as trimethoprim/sulfamethoxazole) may lead to increases in serum potassium. Monitoring of potassium should be undertaken as appropriate.

Thiazides have been shown to increase the urinary excretion of magnesium, which may result in hypomagnesaemia.

Metabolic and endocrine effects
Treatment with a thiazide diuretic may impair glucose tolerance. Dose adjustment of antidiabetic medicinal products, including insulin, may be required. Latent diabetes mellitus may become manifest during thiazide therapy. Increases in cholesterol and triglyceride levels have been associated with thiazide diuretic therapy. At the doses contained in Candesartan Hydrochlorothiazide, only minimal effects were observed. Thiazide diuretics increase serum uric acid concentration and may precipitate gout in susceptible patients.

Photosensitivity
Cases of photosensitivity reactions have been reported during use of thiazide diuretics (see section 4.8). If a photosensitivity reaction occurs, it is recommended to stop treatment. If re-administration of treatment is essential, it is recommended to protect areas exposed to the sun or to artificial UVA radiation.

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

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)
There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended (see sections 4.5 and 5.1).

If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure.

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

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 medicinal products that affect this system including AIIRAs, has been associated with acute hypotension, azotaemia, uraemia, 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.
Hypersensitivity reactions to hydrochlorothiazide may occur in patients with or without a history of allergy or bronchial asthma, but are more likely in patients with such a history.
Exacerbation or activation of systemic lupus erythaematosus has been reported with the use of thiazide diuretics.

The antihypertensive effect of Candesartan Hydrochlorothiazide may be enhanced by other antihypertensives.

Choroidal effusion, acute myopia and secondary *angle-closure glaucoma*:

Hydrochlorothiazide, a sulfonamide, can cause an idiosyncratic reaction resulting in choroidal effusion with visual field defect, transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of drug initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue drug intake as rapidly as possible. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulfonamide or penicillin allergy

Non-melanoma skin cancer
An increased risk of non-melanoma skin cancer (NMSC) [basal cell carcinoma (BCC) and squamous cell carcinoma (SCC)] with increasing cumulative dose of hydrochlorothiazide (HCTZ) exposure has been observed in two epidemiological studies based on the Danish National Cancer Registry. Photosensitizing actions of HCTZ could act as a possible mechanism for NMSC.

Patients taking HCTZ should be informed of the risk of NMSC and advised to regularly check their skin for any new lesions and promptly report any suspicious skin lesions. Possible preventive measures such as limited exposure to sunlight and UV rays and, in case of exposure, adequate protection should be advised to the patients in order to minimize the risk of skin cancer. Suspicious skin lesions should be promptly examined potentially including histological examinations of biopsies. The use of HCTZ may also need to be reconsidered in patients who have experienced previous NMSC (see also section 4.8).

Acute Respiratory Toxicity
Very rare severe cases of acute respiratory toxicity, including acute respiratory distress syndrome (ARDS) have been reported after taking hydrochlorothiazide. Pulmonary oedema typically develops within minutes to hours after hydrochlorothiazide intake. At the onset, symptoms include dyspnoea, fever, pulmonary deterioration and hypotension. If diagnosis of ARDS is suspected, Candesartan Hydrochlorothiazide should be withdrawn and appropriate treatment given. Hydrochlorothiazide should not be administered to patients who previously experienced ARDS following hydrochlorothiazide intake.

This medicinal product contains lactose, as an excipient, and patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

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

The potassium depleting effect of hydrochlorothiazide could be expected to be potentiated by other medicinal products associated with potassium loss and hypokalaemia (e.g. other kaliuretic diuretics, laxatives, amphotericin, carbenoxolone, penicillin G sodium, salicylic acid derivates, steroids, ACTH).

Concomitant use of Candesartan Hydrochlorothiazide and potassium-sparing diuretics, potassium supplements or salt substitutes or other medicinal products that may increase serum potassium levels (e.g. heparin sodium, co-trimoxazole also known as trimethoprim/sulfamethoxazole) may lead to increases in serum potassium. Monitoring of potassium should be undertaken as appropriate (see section 4.4).

Diuretic-induced hypokalaemia and hypomagnesaemia predisposes to the potential cardiotoxic effects of digitalis glycosides and antiarrhythmics. Periodic monitoring of serum potassium is recommended when Candesartan Hydrochlorothiazide is administered with such medicinal products, and with the following medicinal products that could induce torsades de pointes:

- Class Ia antiarrhythmics (e.g. quinidine, hydroquinidine, disopyramide)
- Class III antiarrhythmics (e.g. amiodarone, sotalol, dofetilide, ibutilide)
- Some antipsychotics (e.g. thioridazine, chlorpromazine, levomepromazine, trifluoperazine, cyamemazine, sulpiride, sultopride, amisulpride, tiapride, pimozide, haloperidol, droperiodol)
- Others (e.g. bepridil, cisapride, diphemanil, erythromycin iv, halofantrin, ketanserin, mizolastin, pentamidine, sparfloxacine, terfenadine, vincamine iv)

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with Angiotensin Converting Enzyme (ACE) inhibitors or hydrochlorothiazide. A similar effect has also been reported with AIIRAs. Use of candesartan and hydrochlorothiazide with lithium is not recommended. If the combination proves necessary, careful monitoring of serum lithium levels is recommended.

When AIIRAs are administered simultaneously with non-steroidal anti-inflammatory drugs (NSAIDs) (i.e. selective COX-2 inhibitors, acetylsalicylic acid (> 3 g/day) and non-selective NSAIDs), attenuation of the antihypertensive effect may occur.

As with ACE inhibitors, concomitant use of AIIRAs and NSAIDs may lead to an increased risk of worsening of renal function, including possible acute renal failure, and an increase in serum potassium, especially in patients with poor pre-existing renal function. The combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring renal function after initiation of concomitant therapy, and periodically thereafter.

The diuretic, natriuretic and antihypertensive effect of hydrochlorothiazide is blunted by NSAIDs.

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

The absorption of hydrochlorothiazide is reduced by colestipol or cholestyramine.

The effect ofnondepolarising skeletal muscle relaxants (e.g. tubocurarine) may be potentiated by hydrochlorothiazide.

Thiazide diuretics may increase serum calcium levels due to decreased excretion. If calcium supplements or Vitamin D must be prescribed, serum calcium levels should be monitored and the dose adjusted accordingly.

The hyperglycaemic effect of beta-blockers and diazoxide may be enhanced by thiazides.

Anticholinergic agents (e.g. atropine, biperiden) may increase the bioavailability of thiazide-type diuretics by decreasing gastrointestinal motility and stomach emptying rate.

Thiazide may increase the risk of adverse effects caused by amantadine.

Thiazides may reduce the renal excretion of cytotoxic medicinal products (e.g. cyclophosphamide, methotrexate) and potentiate their myelosuppressive effects.

Postural hypotension may become aggravated by simultaneous intake of alcohol, barbiturates or anaesthetics.

Treatment with a thiazide diuretic may impair glucose tolerance. Dose adjustment of antidiabetic medicinal products, including insulin, may be required. Metformin should be used with caution because of the risk of lactic acidosis induced by possible functional renal failure linked to hydrochlorothiazide.

Hydrochlorothiazide may cause the arterial response to pressor amines (e.g. adrenaline) to decrease but not enough to exclude a pressor effect.

Hydrochlorothiazide may increase the risk of acute renal insufficiency especially with high doses of iodinated contrast media.

Concomitant treatment with cyclosporine may increase the risk of hyperuricaemia and gout-type complications.

Concomitant treatment with baclofen, amifostin, tricyclic antidepressants or neuroleptics may lead to enhancement of the antihypertensive effect and may induce hypotension.

4.6 Fertility, pregnancy and lactation

Pregnancy

Angiotensin II Receptor Antagonists (AIIRAs):
The use of AIIRAs is not recommended during the first trimester of pregnancy (see section 4.4). The use of AIIRAs is contraindicated during the second and third trimester of pregnancy (see section 4.3 and 4.4).

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however, a small increase in risk cannot be excluded. Whilst there is no controlled epidemiological data on the risk with AIIRAs, similar risks may exist for this class of drugs. Unless continued AIIRA therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with AIIRAs should be stopped immediately and, if appropriate, alternative therapy should be started.

Exposure to AIIRA therapy during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia) (see section 5.3).
Should exposure to AIIRAs have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.
Infants whose mothers have taken AIIRAs should be closely observed for hypotension (see sections 4.3 and 4.4).

Hydrochlorothiazide:
There is limited experience with hydrochlorothiazide during pregnancy, especially during the first trimester. Animal studies are insufficient.
Hydrochlorothiazide crosses the placenta. Based on the pharmacological mechanism of action of hydrochlorothiazide its use during the second and third trimesters may compromise foeto-placental perfusion and may cause foetal and neonatal effects like icterus, disturbance of electrolyte balance and thrombocytopenia.
Hydrochlorothiazide should not be used for gestational oedema, gestational hypertension or preeclampsia due to the risk of decreased plasma volume and placental hypoperfusion, without a beneficial effect on the course of the disease.
Hydrochlorothiazide should not be used for essential hypertension in pregnant women except in rare situations where no other treatment could be used.

Breastfeeding

Angiotensin II Receptor Antagonists (AIIRAs):
Because no information is available regarding the use of candesartan during breastfeeding, candesartan is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.

Hydrochlorothiazide:
Hydrochlorothiazide is excreted in human milk in small amounts. Thiazides in high doses causing intense diuresis can inhibit the milk production. The use of hydrochlorothiazide during breast-feeding is not recommended. If hydrochlorothiazide is used during breast-feeding, doses should be kept as low as possible.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. When driving vehicles or operating machines, it should be taken into account that occasionally dizziness or weariness may occur during treatment with Candesartan Hydrochlorothiazide.

4.8 Undesirable effects

In controlled clinical studies with candesartan cilexetil/hydrochlorothiazide adverse reactions were mild and transient. Withdrawals from treatment due to adverse events were similar with candesartan cilexetil/hydrochlorothiazide (2.3-3.3%) and placebo (2.7-4.3%).

In clinical trials with candesartan cilexetil/hydrochlorothiazide, adverse reactions were limited to those that were reported previously with candesartan cilexetil and/or hydrochlorothiazide.

The table below presents adverse reactions with candesartan cilexetil from clinical trials and post marketing experience. In a pooled analysis of clinical trial data of hypertensive patients, adverse reactions with candesartan cilexetil were defined based on an incidence of adverse events with candesartan cilexetil at least 1% higher than the incidence seen with placebo:

The frequencies used in the tables throughout section 4.8 are: very common (≥ 1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000) and not known (cannot be estimated from the available data).

System Organ Class	Frequency	Undesirable Effect
Infections and infestations	Common	Respiratory infection
Blood and lymphatic system disorders	Very rare	Leukopenia, neutropenia and agranulocytosis
Metabolism and nutrition disorders	Very rare	Hyperkalaemia, hyponatraemia
Nervous system disorders	Common	Dizziness/vertigo, headache
Respiratory, thoracic and mediastinal disorders	Very rare	Cough
Gastrointestinal disorders	Very rare	Nausea
	Not known	Diarrhoea
Hepatobiliary disorders	Very rare	Increased liver enzymes, abnormal hepatic function or hepatitis
Skin and subcutaneous tissue disorders	Very rare	Angioedema, rash, urticaria, pruritus
Musculoskeletal and connective tissue disorders	Very rare	Back pain, arthralgia, myalgia
Renal and urinary disorders	Very rare	Renal impairment, including renal failure in susceptible patients (see section 4.4)

The table below presents adverse reactions with hydrochlorothiazide monotherapy usually with doses of 25 mg or higher.

System Organ Class	Frequency	Undesirable Effect
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Not known	Non-melanoma skin cancer (Basal cell carcinoma and Squamous cell carcinoma)
Blood and lymphatic system disorders	Rare	Leukopenia, neutropenia/agranulocytosis, thrombocytopenia, aplastic anaemia, bone marrow depression, haemolytic anaemia
Immune system disorders	Rare	Anaphylactic reactions
Metabolism and nutrition disorders	Common	Hyperglycaemia, hyperuricaemia, electrolyte imbalance (including hyponatraemia and hypokalaemia)
Psychiatric disorders	Rare	Sleep disturbances, depression, restlessness
Nervous system disorders	Common	Light-headedness, vertigo
	Rare	Paraesthesia
Eye disorders	Rare	Transient blurred vision
	Not known	Acute myopia, acute angle-closure glaucoma, choroidal effusion

Cardiac disorders	Rare	Cardiac arrhythmias
Vascular disorders	Uncommon	Postural hypotension
	Rare	Necrotising angiitis (vasculitis, cutaneous vasculitis)
Respiratory, thoracic and mediastinal disorders	Rare	Respiratory distress (including pneumonitis and pulmonary oedema)
	Very rare	Acute respiratory distress syndrome (ARDS) (see section 4.4)
Gastrointestinal disorders	Uncommon	Anorexia, loss of appetite, gastric irritation, diarrhoea, constipation
	Rare	Pancreatitis
Hepatobiliary disorders	Rare	Jaundice (intrahepatic cholestatic jaundice)
Skin and subcutaneous tissue disorders	Uncommon	Rash, urticaria, photosensitivity reactions
	Rare	Toxic epidermal necrolysis,
	Not known	Systemic lupus erythematosus. Cutaneous lupus erythematosus
Musculoskeletal and connective tissue disorders	Rare	Muscle spasm
Renal and urinary disorders	Common	Glycosuria
	Rare	Renal dysfunction and interstitial nephritis
General disorders and administration site conditions	Common	Weakness
	Rare	Fever
Investigations	Common	Increases in cholesterol and triglycerides
	Rare	Increases in BUN and serum creatinine

Description of selected adverse reactions
Non-melanoma skin cancer: Based on available data from epidemiological studies, cumulative dose-dependent association between HCTZ and NMSC has been observed (see also sections 4.4 and 5.1).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Website: www.hpra.ie

4.9 Overdose

Symptoms
Based on pharmacological considerations, the main manifestation of an overdose of candesartan cilexetil 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.

The main manifestation of an overdose of hydrochlorothiazide is acute loss of fluid and electrolytes. Symptoms such as dizziness, hypotension, thirst, tachycardia, ventricular arrhythmias, sedation/impairment of consciousness and muscle cramps can also be observed.

Management
No specific information is available on the treatment of overdose with Candesartan Hydrochlorotiazide tablets. The following measures are, however, suggested in case of overdosage.
When indicated, induction of vomiting or gastric lavage should be considered. 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 isotonic saline solution. Serum electrolyte and acid balance should be checked and corrected, if needed. Sympathomimetic medicinal products may be administered if the above-mentioned measures are not sufficient.
Candesartan cannot be removed by haemodialysis. It is not known to what extent hydrochlorothiazide is removed by haemodialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Angiotensin II antagonists + diuretics, ATC code C09DA06

Mechanism of Action
Angiotensin II is the primary vasoactive hormone of the renin-angiotensin-aldosterone system and plays a role in the pathophysiology of hypertension and other cardiovascular disorders. It also has a role in the pathogenesis of organ hypertrophy and end organ 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_1) receptor.

Pharmacodynamic effects
Candesartan cilexetil is a prodrug which is rapidly converted to the active drug, candesartan, by ester hydrolysis during absorption from the gastrointestinal tract. Candesartan is an AIIRA, selective for AT_1 receptors, with tight binding to and slow dissociation from the receptor. It has no agonist activity.

Candesartan does not influence ACE or other enzyme systems usually associated with the use of ACE inhibitors. Since there is no effect on the degradation of kinins, or on the metabolism of other substances, such as substance P, AIIRAs are unlikely to be associated with cough. In controlled clinical trials comparing candesartan cilexetil with ACE inhibitors, the incidence of cough was lower in patients receiving candesartan cilexetil. Candesartan does not bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.
The antagonism of the AT_1 receptors results in dose related increases in plasma renin levels, angiotensin I and angiotensin II levels, and a decrease in plasma aldosterone concentration.

Clinical efficacy and safety
The effects of candesartan cilexetil 8-16 mg (mean dose 12 mg) once daily on cardiovascular morbidity and mortality were evaluated in a randomised clinical trial with 4,937 elderly patients (aged 70-89 years, 21% aged 80 or above) with mild to moderate hypertension followed for a mean of 3.7 years (Study on Cognition and Prognosis in the Elderly). Patients received candesartan or placebo with other antihypertensive treatment added as needed. The blood pressure was reduced from 166/90 to 145/80 mmHg in the candesartan group, and from 167/90 to 149/82 mmHg in the control group. There was no statistically significant difference in the primary endpoint, major cardiovascular events (cardiovascular mortality, non-fatal stroke and non-fatal myocardial infarction). There were 26.7 events per 1000 patient-years in the candesartan group versus 30.0 events per 1000 patient-years in the control group (relative risk 0.89, 95% CI 0.75 to 1.06, p=0.19).

Hydrochlorothiazide inhibits the active reabsorption of sodium, mainly in the distal kidney tubules, and promotes the excretion of sodium, chloride and water. The renal excretion of potassium and magnesium increases dose-dependently, while calcium is reabsorbed to a greater extent. Hydrochlorothiazide decreases plasma volume and extracellular fluid and reduces cardiac output and blood pressure. During long-term therapy, reduced peripheral resistance contributes to the blood pressure reduction.

Large clinical studies have shown that long-term treatment with hydrochlorothiazide reduces the risk for cardiovascular morbidity and mortality.
Candesartan and hydrochlorothiazide have additive antihypertensive effects.

In hypertensive patients, candesartan cilexetil/hydrochlorothiazide tablets result in a dose-dependent and long-lasting reduction in arterial blood pressure without reflex increase in heart rate. There is no indication of serious or exaggerated first dose hypotension or rebound effect after cessation of treatment. After administration of a single dose of candesartan cilexetil/hydrochlorothiazide tablets, onset of the antihypertensive effect generally occurs within 2 hours.
With continuous treatment, most of the reduction in blood pressure is attained within four weeks and is sustained during long-term treatment. Candesartan cilexetil/hydrochlorothiazide tablets 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 a double-blind randomised study, candesartan cilexetil/hydrochlorothiazide 16 mg/12.5 mg tablets once daily reduced blood pressure significantly more, and controlled significantly more patients, than the combination losartan/hydrochlorothiazide 50 mg/12.5 mg once daily.

In double-blind, randomised studies, the incidence of adverse events, especially cough, was lower during treatment with candesartan cilexetil/hydrochlorothiazide than during treatment with combinations of ACE inhibitors and hydrochlorothiazide.

In two clinical studies (randomised, double-blind, placebo controlled, parallel group) including 275 and 1524 randomised patients**,** respectively, the candesartan cilexetil/hydrochlorothiazide combinations 32 mg/12.5 mg and 32 mg/25 mg resulted in blood pressure reductions of 22/15 mmHg and 21/14 mmHg, respectively, and were significantly more effective than the respective monocomponents.

In a randomised, double-blind, parallel group clinical study including 1975 randomised patients not optimally controlled on 32 mg candesartan cilexetil once daily, the addition of 12.5 mg or 25 mg hydrochlorothiazide resulted in additional blood pressure reductions. The candesartan cilexetil/hydrochlorothiazide combination 32 mg/25 mg was significantly more effective than the 32 mg/12.5 mg combination, and the overall mean blood pressure reductions were 16/10 mmHg and 13/9 mmHg, respectively.

Candesartan cilexetil/hydrochlorothiazide is similarly effective in patients irrespective of age and gender.

Currently there are no data on the use of candesartan cilexetil/hydrochlorothiazide in patients with renal disease/nephropathy, reduced left ventricular function/congestive heart failure and post myocardial infarction.

Two large randomised, controlled trials (ONTARGET (Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) and VA NEPHRON-D (The Veterans Affairs Nephrology in Diabetes)) have examined the use of the combination of an ACE-inhibitor with an angiotensin II receptor blocker.

ONTARGET was a study conducted in patients with a history of cardiovascular or cerebrovascular disease, or type 2 diabetes mellitus accompanied by evidence of end-organ damage. VA NEPHRON-D was a study in patients with type 2 diabetes mellitus and diabetic nephropathy.

These studies have shown no significant beneficial effect on renal and/or cardiovascular outcomes and mortality, while an increased risk of hyperkalaemia, acute kidney injury and/or hypotension as compared to monotherapy was observed. Given their similar pharmacodynamic properties, these results are also relevant for other ACE-inhibitors and angiotensin II receptor blockers. ACE-inhibitors and angiotensin II receptor blockers should therefore not be used concomitantly in patients with diabetic nephropathy.

ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints) was a study designed to test the benefit of adding aliskiren to a standard therapy of an ACE-inhibitor or an angiotensin II receptor blocker in patients with type 2 diabetes mellitus and chronic kidney disease, cardiovascular disease, or both. The study was terminated early because of an increased risk of adverse outcomes. Cardiovascular death and stroke were both numerically more frequent in the aliskiren group than in the placebo group and adverse events and serious adverse events of interest (hyperkalaemia, hypotension and renal dysfunction) were more frequently reported in the aliskiren group than in the placebo group.

Non-melanoma skin cancer
Based on available data from epidemiological studies, cumulative dose-dependent association between HCTZ and NMSC has been observed. One study included a population comprised of 71,533 cases of BCC and of 8,629 cases of SCC matched to 1,430,833 and 172,462 population controls, respectively. High HCTZ use (≥50,000 mg cumulative) was associated with an adjusted OR of 1.29 (95% CI: 1.23-1.35) for BCC and 3.98 (95% CI: 3.68-4.31) for SCC. A clear cumulative dose response relationship was observed for both BCC and SCC. Another study showed a possible association between lip cancer (SCC) and exposure to HCTZ: 633 cases of lip-cancer were matched with 63,067 population controls, using a risk-set sampling strategy. A cumulative dose-response relationship was demonstrated with an adjusted OR 2.1 (95% CI: 1.7-2.6) increasing to OR 3.9 (3.0-4.9) for high use (~25,000 mg) and OR 7.7 (5.7-10.5) for the highest cumulative dose (~100,000 mg) (see also section 4.4).

5.2 Pharmacokinetic properties

Concomitant administration of candesartan cilexetil and hydrochlorothiazide has no clinically significant effect on the pharmacokinetics of either medicinal product.

Absorption and distribution

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

Hydrochlorothiazide
Hydrochlorothiazide is rapidly absorbed from the gastrointestinal tract with an absolute bioavailability of approximately 70%. Concomitant intake of food increases the absorption by approximately 15%. The bioavailability may decrease in patients with cardiac failure and pronounced oedema.

The plasma protein binding of hydrochlorothiazide is approximately 60%. The apparent volume of distribution is approximately 0.8 l/kg.

Biotransformation and elimination

Candesartan cilexetil
Candesartan is mainly eliminated unchanged via urine and bile and only to a minor extent eliminated by hepatic metabolism (CYP2C9). Available interaction studies indicate no effect on CYP2C9 and CYP3A4. Based on *in vitro* data, no interaction would be expected to occur *in vivo* with medicinal products whose metabolism is dependent upon cytochrome P450 isoenzymes CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1 or CYP3A4. The terminal half-life ($t_{½}$) of candesartan is approximately 9 hours. There is no accumulation following multiple doses. The half-life of candesartan remains unchanged (approximately 9 h) after administration of candesartan cilexetil in combination with hydrochlorothiazide. No additional accumulation of candesartan occurs after repeated doses of the combination compared to monotherapy.

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

Hydrochlorothiazide
Hydrochlorothiazide is not metabolised and is excreted almost entirely as unchanged drug by glomerular filtration and active tubular secretion. The terminal $t_{½}$ of hydrochlorothiazide is approximately 8 hours. Approximately 70% of an oral dose is eliminated in the urine within 48 hours. The half-life of hydrochlorothiazide remains unchanged (approximately 8 h) after administration of hydrochlorothiazide in combination with candesartan cilexetil. No additional accumulation of hydrochlorothiazide occurs after repeated doses of the combination compared to monotherapy.

Pharmacokinetics in special populations

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

In patients with mild to moderate renal impairment, C_{max} and AUC of candesartan increased during repeated dosing by approximately 50% and 70%, respectively, but the terminal $t_{½}$ 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 $t_{½}$ of candesartan was approximately doubled in patients with severe renal impairment. The pharmacokinetics in patients undergoing haemodialysis were similar to those in patients with severe renal impairment.

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

Hydrochlorothiazide
The terminal $t_{½}$ of hydrochlorothiazide is prolonged in patients with renal impairment.

5.3 Preclinical safety data

There were no qualitative new toxic findings with the combination compared to that observed for each component. In preclinical safety studies candesartan itself had effects on the kidneys and on red cell parameters at high doses in mice, rats, dogs and monkeys. Candesartan caused a reduction of red blood cell parameters (erythrocytes, haemoglobin, haematocrit). Effects on the kidneys (such as regeneration, dilatation and basophilia in tubules; increased plasma concentrations of urea and creatinine) were induced by candesartan which could be secondary to the hypotensive effect leading to alterations of renal perfusion. Addition of hydrochlorothiazide potentiates the nephrotoxicity of candesartan. Furthermore, candesartan induced

hyperplasia/hypertrophy of the juxtaglomerular cells. These changes were considered to be caused by the pharmacological action of candesartan and to be of little clinical relevance.

Foetotoxicity has been observed in late pregnancy with candesartan. The addition of hydrochlorothiazide did not significantly affect the outcome of foetal development studies in rats, mice or rabbits (see section 4.6).

Candesartan and hydrochlorothiazide both show genotoxic activity at very high concentrations/doses. Data from *in vitro* and *in vivo* genotoxicity testing indicate that candesartan and hydrochlorothiazide are unlikely to exert any mutagenic or clastogenic activity under conditions of clinical use.

There was no evidence that either compound is carcinogenic.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Maize starch
Hydroxypropylcellulose
Croscarmellose sodium
Magnesium stearate
Triethyl Citrate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC-PVDC/Al blister
Pack sizes: 7, 14, 28, 30, 56, 70, 90, 98, 100 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused product or waste should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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Euro Business Park
Little Island
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Ireland

8 MARKETING AUTHORISATION NUMBER

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