SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Atacand plus 16/12,5 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 16 mg candesartan cilexetil and 12.5 mg hydrochlorothiazide.

Excipient(s) with known effect

Each tablet contains 68 mg Lactose monohydrate

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets

Atacand plus 16/12,5 mg tablet (with score line): A peach, oval, biconvex tablet, with a score and engraved $\frac{A}{CS}$ on one side and a score on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Atacand plus is indicated for the treatment of essential hypertension when monotherapy is not sufficiently effective.

4.2 Posology and method of administration

Posology

Usual dosage

The recommended dose is 1 Atacand plus 16/12,5 mg tablet once daily. The peak antihypertensive effect is attained within 4 weeks of initiation of treatment.

Special dosage instructions

Elderly patients

No dose adjustment is required in elderly patients.

Patients with impaired renal function

In patients with mild to moderate renal dysfunction (i.e. creatinine clearance 30-89 ml/min/1,73m^2 body surface area), dose titration is recommended.

In patients with renal impairment, loop diuretics should be preferred to thiazides.

The combination of an ACE inhibitor, a potassium-sparing diuretic and Atacand plus is not recommended and should only be considered after careful assessment of the potential benefit and the potential risks.

Patients with severe renal dysfunction (i.e. creatinine clearance <30 ml/min/1.73 m^2 body surface area) should not be administered Atacand plus.

Patients with impaired hepatic function

Dose titration is recommended in patients with mild to moderate chronic liver disease. Atacand plus should not be administered to patients with severe hepatic impairment and/or cholestasis.

Children and adolescents

Safety and efficacy of Atacand plus have not been investigated in children and adolescents (aged 0-18 years).

Method of administration

Atacand plus may be taken with or without food.

4.3 Contraindications

Atacand plus is contraindicated in cases of hypersensitivity to the active substances or sulfonamide derivatives (hydrochlorothiazide is a sulfonamide derivative), to any of the excipients and during pregnancy and lactation.

Candesartan is contraindicated in patients with hereditary angioedema or those having developed angioedema during previous treatment with an ACE inhibitor or angiotensin-II-receptor antagonist.

Atacand plus must likewise not be taken in cases of severe renal dysfunction (i.e. creatinine clearance <30 ml/min/ 1,73 m² body severe area), severe hepatic dysfunction, cholestasis and gout. Atacand plus should also not be taken in cases of therapy-resistant hypokalaemia, hyponatraemia, hypercalcaemia and anuria.

Concomitant use of ACE inhibitors or angiotensin-II-receptor antagonists (e.g. Atacand plus) with medicinal products containing aliskiren is contraindicated in patients with diabetes mellitus or impaired renal function (GFR <60 ml/min/1,73m^2).

4.4 Warnings and precautions

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

There is evidence that the concomitant use of ACE inhibitors, angiotensin-II-receptor antagonists or aliskiren increases the risk of hypotension, hyperkalaemia and a decrease in renal function (including acute renal failure). Dual RAAS blockade through the concomitant use of ACE inhibitors, angiotensin-II-receptor antagonists or aliskiren is therefore not recommended (see section "Interactions").

When therapy with dual RAAS blockade is considered absolutely necessary, this should proceed only under specialist supervision and with close monitoring of renal function, electrolyte levels and blood pressure.

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

Patients with renal artery stenosis

Other medicinal products that affect the renin-angiotensin-aldosterone system, such as ACE inhibitors, may increase blood urea and serum creatinine levels in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney. This might also occur with angiotensin-II-receptor antagonists.

Intravascular hypovolaemia

In patients with intravascular hypovolaemia and/or sodium losses, symptomatic hypotension may occur, as is known with other medicinal products that act on the renin-angiotensin-aldosterone system. For this reason, this condition should be corrected prior to initiation of treatment with Atacand plus.

Anaesthesia and surgical procedures

In patients treated with angiotensin-II-receptor antagonists, hypotension may occur during anaesthesia and surgical procedures due to blockade of the renin-angiotensin system. Very rarely, hypotension may be so serious as to warrant intravenous administration of fluid and/or a vasopressor.

Renal impairment

Changes to renal function may occur in predisposed patients treated with Atacand plus, as well as with other substances that inhibit the renin-angiotensin-aldosterone system (see "Contraindications").

In patients with renal impairment treated with Atacand plus, periodic monitoring of potassium, creatinine and uric acid levels is recommended. In the patient group with severe renal impairment, a loop diuretic should be preferred to thiazides.

Renal transplantation

There is limited clinical evidence in the use of Atacand plus in patients with renal transplantation.

Aortic and mitral valve stenosis or obstructive hypertrophic cardiomyopathy

As with the use of other vasodilators, special caution is indicated in patients suffering from haemodynamically relevant aortic or mitral valve stenosis or obstructive hypertrophic cardiomyopathy.

Electrolyte imbalances

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

Based on experience with other medicinal products that affect the renin-angiotensin-aldosterone system, concomitantly administered ACE inhibitors, aliskiren, potassium-sparing diuretics, medicines containing potassium (as a supplement or potassium salt substitution) and other medicinal products that can increase the potassium serum level (e.g. heparin, co-trimoxazole), may lead to increased potassium serum levels.

Hydrochlorothiazide dose-dependently increases renal potassium excretion and can thus cause hypokalaemia. This effect of hydrochlorothiazide seems to be less significant in combination with candesartan cilexetil. The risk of hypokalaemia can be increased in patients with cirrhosis of the liver, in patients with excessive diuresis, in patients with inadequate oral absorption of electrolytes and with concomitant administration of steroids or adrenocorticotropic hormone (ACTH).

Metabolic and endocrine effects

Treatment with thiazide diuretics may worsen glucose tolerance. A dose adjustment of antidiabetic agents, including insulin, may be required. Latent diabetes mellitus may become manifest during thiazide treatment. An increase in cholesterol and triglyceride levels has been

observed with thiazide diuretic treatment. At the amounts of hydrochlorothiazide contained in Atacand plus, only minimal such effects have been observed.

Marked hypercalcaemia can be a sign of latent hyperparathyroidism. Thiazides should be stopped before carrying out thyroid function tests.

Thiazide diuretics increase serum uric acid concentration and may precipitate a gout attack in patients at risk.

Angioedema

In patients treated with candesartan, angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been observed in very rare cases. In these cases, Atacand plus should be discontinued immediately and the patient carefully monitored until the swelling has resolved. Patients with a history of angioedema unrelated to antihypertensive therapy could be exposed to a higher risk of angioedema induced by therapy with Atacand plus (see "Contraindications").

Non-melanoma skin cancer

In two epidemiological studies based on the Danish National Cancer Registry, an increased risk of non-melanoma skin cancer (NMSC), in the form of basal cell and squamous cell carcinoma (BCC and SCC), has been observed with increasing cumulative hydrochlorothiazide (HCTZ) exposure. The photosensitising action of HCTZ could be involved as a possible mechanism for NMSC development.

Patients using HCTZ should be informed of the risk of NMSC and advised to regularly check their skin for new lesions and to promptly report any suspicious skin changes. Preventive measures such as limited sunlight/UV exposure and, in the event of exposure, adequate sun protection should be recommended to patients in order to minimise the risk of skin cancer. Suspicious skin changes should be promptly examined, potentially via histological examinations of biopsies. The use of HCTZ may also need to be reconsidered in patients with a previous history of NMSC (see also section "Undesirable effects").

Choroidal effusion, acute myopia and secondary angle-closure glaucoma

Medicinal products containing hydrochlorothiazide can trigger an idiosyncratic reaction that can lead to choroidal effusion with visual field defects, transient myopia and acute angle-closure glaucoma. Symptoms include rapid onset of decreased visual acuity or eye pain and typically appear within hours to weeks after the start of therapy. Untreated angle closure glaucoma can lead to permanent loss of vision. Primary therapy consists of immediate discontinuation of the medicinal product. If intraocular pressure remains elevated, immediate medical treatment or

surgery must be considered. Risk factors for developing angle-closure glaucoma may be a history of sulphonamide or penicillin allergy.

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 taking hydrochlorothiazide. At the onset, symptoms include dyspnoea, fever, worsening lung function and hypotension. If ARDS is suspected, Atacand plus should be discontinued and appropriate treatment instituted. Hydrochlorothiazide must not be used in patients who have previously experienced ARDS after taking hydrochlorothiazide.

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 renal disease, including renal artery stenosis), changes such as acute hypotension, azotaemia, oliguria or, rarely, acute renal impairment, may be observed during concomitant treatment with other medicinal products that act on this system.

As with all antihypertensive agents, an excessive decrease in blood pressure in patients with ischaemic heart disease or atherosclerotic cerebrovascular disease may lead to myocardial infarction or stroke.

Hypersensitivity reactions to hydrochlorothiazide may occur in patients with or without a history of allergy such as bronchial asthma but are more likely in patients with such a history.

Exacerbation or activation of systemic lupus erythematosus has been reported in association with the use of thiazide diuretics.

This medicinal product contains lactose as an excipient. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucosegalactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Candesartan cilexetil

In vitro interaction studies indicate that CYP2C9 and CYP3A4 are not inhibited by candesartan.

Based on *in vitro* trial data, no interactions are expected *in vivo* with medicinal products whose metabolism is dependent upon cytochrome P450 isoenzymes CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1 or CYP3A4.

Active substances investigated with candesartan cilexetil in clinical pharmacokinetic studies include hydrochlorothiazide, warfarin, digoxin, oral contraceptives (e.g. ethinylestradiol/levonorgestrel), glibenclamide, nifedipine and enalapril. No pharmacokinetic interactions of clinical relevance were identified in these studies.

As most of the enzymes involved in the metabolism of acenocoumarol and phenprocoumon are unknown and interaction with candesartan cilexetil has not been studied, caution is indicated when candesartan cilexetil is taken concomitantly with these anticoagulants. Close monitoring of blood clotting (prothrombin time) is imperative at least at the start of treatment, upon discontinuation of treatment and modifications in dose.

A reversible increase in serum lithium concentrations and lithium toxicity have been observed during concomitant administration of lithium and ACE inhibitors or angiotensin-II-receptor antagonists or thiazides. As thiazides reduce renal lithium clearance, lithium toxicity may be increased after the use of Atacand Plus. Close monitoring of serum lithium concentrations is therefore recommended during concomitant use.

A reduction in hypotension may occur with concomitant administration of angiotensin-II-receptor antagonists, including Atacand, together with non-steroidal anti-inflammatory drugs (NSAIDs), including selective COX-2 inhibitors, acetylsalicylic acid or other non-selective NSAIDs. Combination of ACE inhibitors or angiotensin-II-receptor antagonists with non-steroidal NSAIDs may lead to an increased risk of worsening renal function, including acute renal failure. Particularly in patients with existing renal impairment, elevated serum potassium levels may also occur. The above-mentioned drug combination should be administered with caution, especially in elderly patients. Patients should be adequately hydrated and renal function should be monitored at the start and periodically during treatment.

Dual blockade of the renin-angiotensin-aldosterone system (RAAS) see section “Warnings and precautions”.

The bioavailability of candesartan is not affected by food.

The antihypertensive effect of Atacand plus may be enhanced by other co-administered antihypertensives.

Hydrochlorothiazide

The following substances can lead to interactions if administered concomitantly:

Alcohol, barbiturates, narcotics: increased orthostatic hypotension.

Antidiabetics (oral agents and insulin): dose adjustment of the antidiabetic medication may be necessary.

Other antihypertensives: additive effect.

Digitalis glycosides: Diuretic-induced hypokalaemia and hypomagnesaemia predisposes to the potential cardiotoxic effect of digitalis glycosides and antiarrhythmics. Periodic monitoring of the potassium level is recommended when Atacand plus is co-administered with these substances.

Cholestyramine and colestipol, ion-exchange resins: The absorption of hydrochlorothiazide is reduced by anion-exchange resins. Single doses of cholestyramine or colestipol can bind hydrochlorothiazide and decrease gastrointestinal absorption by as much as 85% and 43%, respectively.

Corticosteroids, ACTH: increase in electrolyte deficiency, especially hypokalaemia.

Hydrochlorothiazide can cause potassium losses. This effect can be potentiated by co-administered substances that can also lead to potassium losses and hypokalaemia (e.g. kaliuretic diuretics, laxatives, amphotericin, carbenoxolone, salicylic acid derivatives).

Catecholamines (e.g. adrenaline): A reduction in the effect of vasopressors is possible. However, this does not preclude their use.

Non-depolarising muscle relaxants (e.g. tubocurarine): Potentiated effect of muscle relaxants is possible.

Lithium: Reversible increases in serum lithium concentrations have been observed during concomitant administration of lithium with ACE inhibitors or hydrochlorothiazide. While these effects have not been found with the use of Atacand plus, there is a possibility of increase in lithium concentrations. Close monitoring of serum lithium levels is recommended during concomitant treatment.

Non-steroidal anti-inflammatory drugs: In some patients, administration of non-steroidal anti-inflammatory drugs can reduce the diuretic, natriuretic and antihypertensive effect of diuretics. In predisposed patients, worsening renal function has been observed in individual cases.

Allopurinol: increased incidence of hypersensitivity reactions to allopurinol.

Antineoplastic agents (e.g. methotrexate, cyclophosphamide): decreased renal excretion of antineoplastic agents.

Amantadine: increased risk of adverse reactions to amantadine.

Anticholinergics (e.g. atropine, biperiden): increased bioavailability of thiazide-type diuretics.

Vitamin D: enhanced increase in serum calcium.

Ciclosporin: increased risk of hyperuricemia and gout-like complications.

Calcium salts: Thiazide-type diuretics can lead to hypercalcaemia due to an increase in tubular calcium reabsorption.

Diazoxide: increase in the hyperglycaemic effect of diazoxide.

Interactions with medicinal products/laboratory investigations

Due to their effect on calcium metabolism, thiazides may influence methods used for parathyroid gland testing.

There are no clinically significant interactions between hydrochlorothiazide and concomitant food intake.

4.6 Pregnancy and lactation

Pregnancy

The use of Atacand plus is contraindicated during pregnancy (see "Contraindications"). Patients receiving Atacand plus treatment must be made aware of this before considering any pregnancy, so that the appropriate options can be discussed with their treating physician. If pregnancy is confirmed, treatment with Atacand plus must be stopped immediately and, if appropriate, alternative therapy should be instituted.

In humans, angiotensin-II-receptor antagonists are known to induce toxic effects in the foetus (impairment of renal function, oligohydramnios, skull ossification retardation) and in the neonate (renal impairment, hypotension, hyperkalaemia).

Experience with hydrochlorothiazide during pregnancy, especially during the first trimester, is limited. Similarly, data from animal studies are not sufficiently available. Hydrochlorothiazide crosses the placenta. Based on the pharmacological mechanism of action of hydrochlorothiazide, impairment of foetoplacental perfusion is possible during use in pregnancy, which may cause effects in the foetus and/or neonate, including jaundice, electrolyte disturbances and thrombocytopenia.

Lactation

It is unknown whether candesartan is excreted in human milk. However, candesartan has been found in the milk of rats. Hydrochlorothiazide passes into breast milk. Atacand plus must not be

administered during breast-feeding. To exclude potential adverse effects on the nursing infant, it is recommended that breast-feeding be discontinued if treatment with Atacand plus should be essential (see “Contraindications”).

4.7 Effects on ability to drive and use machines

No corresponding studies have been performed. Patients must be informed that vertigo or fatigue may commonly occur during treatment and caution is therefore advised while driving and using machines.

4.8 Undesirable effects

Controlled clinical studies with various doses of candesartan cilexetil/hydrochlorothiazide at various doses (candesartan cilexetil up to 32 mg and hydrochlorothiazide up to 25 mg) have shown an adverse effect profile comparable with placebo. The incidence of adverse events has no association with age or gender. Discontinuation of treatment due to adverse events was roughly similar with candesartan cilexetil/hydrochlorothiazide (2,3-3,3%) and placebo (2,7-4,3%).

In a pooled analysis of data from clinical studies, the following common (≥1/100 to <1/10) adverse events with candesartan cilexetil/hydrochlorothiazide were found at an incidence at least 1% higher than with placebo.

The frequencies of undesirable effects are defined as follows: Very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1000, <1/100), rare (≥1/10‘000, <1/1000), very rare (<1/10’000), not known (cannot be estimated from the available data).

Nervous system disorders

Common: Vertigo.

Adverse events of candesartan cilexetil

Infections and infestations

Common: respiratory infections.

Blood and lymphatic system disorders

Very rare: leukopenia, neutropenia, agranulocytosis.

Metabolism and nutrition disorders

Very rare: hyperkalaemia, hyponatraemia.

Nervous system disorders

Common: light-headedness, headache.

Very rare: vertigo.

Vascular disorders

Very rare: hypotension.

Respiratory, thoracic and mediastinal disorders

Very rare: cough.

Gastrointestinal disorders

Very rare: nausea.

Hepatobiliary disorders

Very rare: increased liver enzymes, abnormal hepatic function, hepatitis.

Skin and subcutaneous tissue disorders

Very rare: angioedema, rash, urticaria, pruritus.

Musculoskeletal and connective tissue disorders

Common: back pain

Very rare: arthralgia, myalgia.

Renal and urinary disorders

Very rare: renal impairment, including renal failure in susceptible patients (see "Warnings and precautions").

Investigations

Very rare: increased levels of creatinine, urea and potassium.

Other adverse events observed during clinical studies are: chest pain, albuminuria, fever, paraesthesia, tachycardia, palpitations, creatine phosphokinase increased, hyperglycaemia, hypertriglyceridemia, hyperuricaemia, epistaxis, anxiety, depression, dyspnoea, haematuria, angina pectoris, oedema and myocardial infarction.

The following adverse reactions have been described with *hydrochlorothiazide* monotherapy (usually at dosages of 25 mg or greater):

Neoplasms benign, malignant and unspecified (incl. cysts and polyps)

Not known: non-melanoma skin cancer [NMSC] (basal cell carcinoma [BCC] and squamous cell carcinoma [SCC]).

Blood and lymphatic system disorders

Rare: leukopenia, neutropenia, agranulocytosis, thrombocytopenia (sometimes with purpura), aplastic anaemia, bone marrow depression, haemolytic anaemia.

Immune system disorders

Rare: anaphylactic reactions.

Metabolism and nutrition disorders

Common: hyperglycaemia, hyperuricaemia, electrolyte imbalances (including hyponatraemia, hypokalaemia, hypomagnesaemia, hypercalcaemia).

Rare: worsening of diabetic metabolic status.

Isolated cases: hypochloraemic alkalosis.

Psychiatric disorders

Rare: sleep disturbances, depression, restlessness.

Nervous system disorders

Common: light-headedness, dizziness.

Rare: paraesthesia.

Eye disorders

Rare: transient visual disturbances.

Very rare: acute myopia, acute angle-closure glaucoma.

Not known: choroidal effusion.

Cardiac disorders

Uncommon: orthostatic hypotension, which can be exacerbated by alcohol, anaesthetics or sedatives.

Rare: cardiac arrhythmias, necrotising angiitis (vasculitis).

Respiratory, thoracic and mediastinal disorders

Rare: respiratory complaints, including pneumonitis and pulmonary oedema.

Very rare: acute respiratory distress syndrome (ARDS).

Gastrointestinal disorders

Uncommon: anorexia, loss of appetite, gastrointestinal complaints (including mild nausea, vomiting, abdominal complaints), diarrhoea, constipation.

Rare: pancreatitis.

Hepatobiliary disorders

Rare: jaundice (intrahepatic cholestatic jaundice).

Skin and subcutaneous tissue disorders

Uncommon: rash, urticaria, photosensitisation.

Rare: toxic epidermal necrolysis, systemic lupus erythematosus, cutaneous lupus erythematosus.

Musculoskeletal and connective tissue disorders

Rare: muscle spasms.

Renal and urinary disorders

Common: glycosuria.

Rare: renal dysfunction, interstitial nephritis.

General disorders and administration site conditions

Common: weakness.

Rare: fever, headache.

Investigations

Common: increases in cholesterol and triglycerides.

Rare: increases in BUN and serum creatinine.

Laboratory findings

An increase in creatinine, urea, potassium, uric acid, glucose and ALAT (GPT), as well as a decrease in sodium, have been observed. Isolated cases of a slight decrease in haemoglobin and an increase in ASAT (GOT) have been observed.

Description of selected undesirable effects

Non-melanoma skin cancer (BCC and SCC): Based on the available data from epidemiological studies, a cumulative dose-dependent association between hydrochlorothiazide (HCTZ) exposure and NMSC development has been observed (see also sections “Warnings and precautions” and “Properties/Effects”).

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions.

4.9 Overdose

Signs and symptoms

Based on pharmacological considerations, an overdose of candesartan cilexetil is likely to manifest as hypotension and dizziness. In single case reports with candesartan cilexetil at doses of up to 672 mg, the patients recovered.

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

Treatment

If hypotension occurs, 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. A sympathomimetic agent may be administered if all such measures are insufficient. 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: ATC code: C09DA06

Mechanism of action /Pharmacodynamics

Angiotensin II is the primary vasoactive hormone of the renin-angiotensin-aldosterone system and plays a significant role in the pathophysiology of hypertension and other cardiovascular disorders. It also plays an important role in the pathogenesis of 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 type 1 (AT_1) receptors.

Candesartan cilexetil is a prodrug which is suitable for oral intake. It is rapidly converted to the active substance, candesartan, by ester hydrolysis during absorption in the gastrointestinal tract. Candesartan is an angiotensin-II-receptor antagonist, selective for AT_1 receptors and without agonist activity. Candesartan displays tight binding to and slow dissociation from the receptor.

The antagonistic effect of the angiotensin-II (AT_1) receptor results in a dose-dependent increase in plasma levels of renin, angiotensin I and angiotensin II. The aldosterone plasma concentration is decreased.

Candesartan does not inhibit ACE or other enzyme systems 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, angiotensin-II-receptor antagonists are unlikely to be associated with cough. Controlled clinical studies comparing candesartan cilexetil with ACE inhibitors show that cough was observed less frequently in patients treated with candesartan cilexetil.

Candesartan does not bind or block other hormone receptors or ion channels of importance in cardiovascular regulation.

Hydrochlorothiazide inhibits the active reabsorption of sodium, mainly in the distal 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 leads to a reduction in plasma volume and extracellular fluid, thereby reducing cardiac output and blood pressure.

During long-term therapy, reduced peripheral resistance contributes to the reduction in blood pressure.

Non-melanoma skin cancer (NMSC): Based on the available data from epidemiological studies, a cumulative dose-dependent association between hydrochlorothiazide (HCTZ) exposure and NMSC development has been observed. One study included a population comprised of 71’553 cases of BCC and of 8’629 cases of SCC, as well as 1’430’883 and 172’462 matching controls, respectively. High HCTZ exposure (cumulative dose ≥ 50’000 mg) was associated with

an adjusted Odds Ratio (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 HCTZ exposure and lip carcinoma (SCC): 633 cases of lip carcinoma were compared with 63'067 matching controls using a risk-set sampling strategy. A cumulative dose-response relationship was shown with a rise in adjusted OR from 2.1 (95% CI: 1,7-2,6) to 3,9 (95% CI: 3,0-4,9) at a high cumulative dose (≥ 25'000 mg) and to 7,7 (95% CI: 5,7-10,5) at the highest cumulative dose (≥ 100'000 mg) (see also section "Warnings and precautions").

The two active substances of candesartan and hydrochlorothiazide have an additive antihypertensive effect.

In hypertension, Atacand plus dose-dependently causes a long-lasting reduction in arterial blood pressure without reflex increase in heart rate. There are no indications of serious or exaggerated first-dose hypotension or a rebound effect after cessation of treatment.

After administration of a single dose of Atacand plus, onset of the antihypertensive effect generally occurs within 2 hours. As treatment continues, the maximum reduction in blood pressure is attained within 4 weeks and can be maintained with long-term treatment. Atacand plus brings about an effective and smooth reduction in blood pressure throughout the entire 24-hour dosing interval, with a trough/peak ratio that warrants once-daily administration.

Atacand plus is equally effective in all patients, irrespective of age and gender.

Treatment with Atacand plus showed a lower incidence of adverse events in double-blind, randomised studies. In particular, cough occurred less frequently compared with combination therapies with ACE inhibitors and hydrochlorothiazide.

Clinical efficacy

In the SCOPE study (Study on Cognition and Prognosis in the Elderly), the effects of antihypertensive treatment with candesartan cilexetil on cardiovascular morbidity and mortality, cognitive function and quality of life were investigated in 4'937 elderly patients (aged 70-89 years) with hypertension (systolic blood pressure 160-179 mmHg and/or diastolic blood pressure 90-99 mmHg).

The table shows the study results for the primary endpoint (major cardiovascular events) and its components. Both treatment regimens led to an effective reduction in systolic and diastolic blood pressure and were generally well tolerated. Cognitive function and quality of life were shown to be well maintained in both study arms.

	No. of patients with a first event			
	Candesartan cilexetil* (N=2477)	Control group* (N=2460)	Relative risk (95% CI)	p-value
Major cardiovascular events	242	268	0,89 (0,75-1,06)	0,19
cardiovascular mortality	145	152	0,95 (0,75-1,19)	0,63
non-fatal stroke	68	93	0,72 (0,53-0,99)	0,04
non-fatal myocardial infarction	54	47	1,14 (0,77-1,68)	0,52

* Any previous antihypertensive treatment was standardised to hydrochlorothiazide 12,5 mg once daily before randomisation. In the event of persistent systolic blood pressure values of ≥ 160 mmHg and/or diastolic blood pressure values of ≥ 90 mmHg, other antihypertensive treatment was administered in addition to the double-blind study medication (candesartan cilexetil 8-16 mg or placebo once daily). Such add-on treatment was given to 49% of patients in the candesartan cilexetil group and 66% of patients in the control group.

In two randomised, double-blind, placebo controlled, clinical studies with 275 and 1524 patients, the combination of candesartan cilexetil/hydrochlorothiazide led to significantly greater reductions in blood pressure than the respective single components. At the 32 mg/25 mg dosage strength, a blood pressure reduction of 21/14 mmHg was attained.

In a randomised, double-blind, clinical study with 1975 patients not optimally controlled on once-daily dosing with 32 mg candesartan cilexetil, the addition of 12,5 mg or 25 mg hydrochlorothiazide led to additional reductions in blood pressure. The combination of candesartan cilexetil/hydrochlorothiazide at the 32 mg/25 mg dosage strength was significantly more effective than the one at 32 mg/12,5 mg, with mean blood pressure reductions amounting to 16/10 mmHg and 13/9 mmHg, respectively.

5.2 Pharmacokinetic properties

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

Absorption

Candesartan cilexetil

Following oral administration, candesartan cilexetil is converted to the active substance candesartan. The mean absolute bioavailability of candesartan after oral administration of a candesartan cilexetil solution is approximately 40%. 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 concentration increases linearly with increasing dosages within 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 more than 99% bound to plasma proteins. The apparent volume of distribution of candesartan is 0,1 l/kg.

Hydrochlorothiazide

Hydrochlorothiazide is rapidly absorbed from the gastrointestinal tract. Absolute bioavailability is approximately 70%.

Concomitant food intake can both increase and decrease the absorption rate (by approximately 15%).

Bioavailability is reduced in patients with heart failure and marked oedema.

Hydrochlorothiazide is approximately 60% bound to plasma proteins. The apparent volume of distribution is approximately 0,8 l/kg.

Distribution

See also section “Absorption”.

Metabolism

Candesartan cilexetil

Candesartan is mainly excreted unchanged via urine and bile and eliminated only to a minor extent by hepatic metabolism (CYP2C9). The terminal half-life of candesartan is approximately 9 hours. There is no accumulation following multiple administration.

The half-life of candesartan (approximately 9 hours) remains unchanged upon co-administration of hydrochlorothiazide. No accumulation of candesartan occurs after repeated administration of the combination product 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. Candesartan is renally excreted both by glomerular filtration and active tubular secretion. Following single oral administration of ^{14}C-labelled candesartan cilexetil, approximately 26% of the dose is excreted in the urine as candesartan and 7% as an inactive metabolite. Approximately 56% of the administered 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 half-life for hydrochlorothiazide is approximately 8 hours. Approximately 70% of an orally administered dose is excreted in the urine within 48 hours.

The half-life of hydrochlorothiazide (approximately 8 hours) remains unchanged upon concomitant ingestion of candesartan cilexetil. Compared to monotherapy, no accumulation of hydrochlorothiazide was found after repeated administration of the combination product.

Elimination

See also section ”Metabolism”.

Kinetics in specific patient groups

Candesartan cilexetil

Elderly patients

In elderly patients (over 65 years), C_{max} and AUC of candesartan are increased by approximately 50% and 80%, respectively in comparison to younger patients. The blood pressure response and the incidence of adverse events after administration of Atacand plus are similar in younger and elderly patients (see “Dosage/Administration”).

Renal impairment

In patients with mild to moderate renal dysfunction, an approximately 50% increase in C_{max} and an approximately 70% increase in the AUC of candesartan were observed with repeated dosing, compared to those with normal renal function. However, the terminal half-life was not increased. In patients with severely impaired renal function, an approximately 50% increase in C_{max} and an approximately 110% increase in AUC were observed. The terminal half-life was practically twice as high in these patients.
The pharmacokinetics in patients undergoing haemodialysis were similar to those in patients with severely impaired renal function.

Hepatic impairment

In patients with mild to moderate hepatic dysfunction (Child-Pugh score 6-9), there was an observed mean increase in C_{max} of 64% and in AUC of 78%.
Experience is limited in patients with severe hepatic disease (Child-Pugh score > 9) and/or cholestasis receiving treatment with candesartan cilexetil (see "Dosage/Administration" and "Contraindications").

Hydrochlorothiazide

The terminal half-life of hydrochlorothiazide is prolonged in patients with renal dysfunction.

5.3 Preclinical safety data

No new toxicological data were found for the candesartan cilexetil/hydrochlorothiazide combination in comparison with those for the single components.

Toxicity

In preclinical safety studies, candesartan showed effects on the kidneys and red cell counts at high doses in mice, rats, dogs and monkeys. Candesartan led to a reduction of red blood cell parameters (erythrocytes, haemoglobin, haematocrit). Candesartan also showed effects on the kidneys (tubular regeneration, dilatation and basophilia; increased plasma concentrations of urea and creatinine). This might be a secondary effect of the hypotensive action, leading to alterations of renal perfusion. Addition of hydrochlorothiazide potentiates the nephrotoxicity of candesartan. Furthermore, candesartan led to hyperplasia/hypertrophy of the juxtaglomerular cells. These changes are assumed to be due to the pharmacological action of candesartan and of little clinical relevance.

Reproductive toxicity

Animal studies with candesartan cilexetil have demonstrated late foetal and neonatal injury in the kidney. The underlying mechanism is believed to be pharmacologically mediated through effects on the renin-angiotensin-aldosterone system.

The addition of hydrochlorothiazide did not significantly affect the outcome of foetal development studies in rats, mice or rabbits (see "Pregnancy, lactation").

Mutagenic and tumorigenic potential

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

There is no evidence that either active substance has any tumorigenic potential.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Carboxymethylcellulose calcium (E466)

Hydroxypropyl cellulose (E463)

Lactose monohydrate

Magnesium stearate (E572)

Maize starch

Polyethylene glycol (macrogol) 8000 (E1521)

Yellow iron oxide (E172), ferric oxide, pigment red (E172).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 MONTHS

Do not use this medicine after the expiry date ("EXP") stated on the container.

6.4 Special precautions for storage

Do not store above 30°C.

Keep out of the reach of children.

6.5 Nature and contents of container and special equipment for use, administration or implantation

16/12,5 mg tablets (with score line): 28, 30 and 98 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

AstraZeneca AG, Neuhofstrasse 34, 6340 Baar, Switzerland

8. MARKETING AUTHORISATION NUMBER(S)

Rwanda FDA-HMP-MA-0124

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19 December 2022

10. DATE OF REVISION OF THE TEXT

March 2022