1. NAME OF THE MEDICINAL PRODUCT
Atacand Plus 16/12.5 mg tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
One Atacand Plus tablet contains 16 mg candesartan cilexetil and 12.5 mg hydrochlorothiazide.
Excipient(s) with known effect
Each tablet contains 68 mg lactose monohydrate.
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Tablets.
Atacand Plus 16/12.5 mg tablets are peach, oval, biconvex tablets with a score on both sides and engraved A/CS on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications
Essential hypertension, where monotherapy with candesartan cilexetil or hydrochlorothiazide is not sufficient.

4.2 Posology and method of administration
Dosage
In Hypertension
The recommended dose of Atacand Plus is 1 tablet once daily.
Dose titration with the individual components (candesartan cilexetil and hydrochlorothiazide) is recommended. When clinically appropriate, a direct change from monotherapy to Atacand Plus can be considered. The dose of candesartan cilexetil should be titrated before switching to Atacand Plus. Atacand Plus can be administered in patients whose blood pressure is not optimally controlled with candesartan cilexetil or hydrochlorothiazide monotherapy.
Most of the antihypertensive effect is usually achieved within 4 weeks after starting treatment.

Method of administration:
Oral use.
Atacand Plus 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.

Special populations

Elderly population
No dosage adjustment is needed in elderly patients.

Patients with reduced blood volume

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

Patients with impaired renal function
Dose titration is recommended in patients with mild to moderate renal impairment (creatinine clearance 30-80 ml/min/1.73 m² Body Surface Area (BSA)).
Atacand Plus is contraindicated in patients with severe renal impairment (creatinine clearance < 30 ml/min/1.73 m² BSA) (see section 4.3).

Patients with reduced liver function
Dose titration of candesartan cilexetil is recommended in patients with mild to moderate hepatic impairment before treatment with Atacand Plus (the recommended starting dose of candesartan cilexetil is 2 mg in these patients). Atacand Plus is contraindicated in patients with severe hepatic impairment and/or cholestasis (see section 4.3).

Paediatric population
The safety and efficacy of Atacand Plus have not yet been established in children from birth to adolescents under the age of 18 years. No data is available.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in Section 6.1, or to other sulphonamides. Hydrochlorothiazide is a sulphonamide.
Pregnancy in the second or third trimester (see Sections 4.4 and 4.6).
Severe renal impairment (creatinine clearance < 30 ml/min/1.73 m^2 BSA).
Severely impaired liver function and/or cholestasis.
Refractory hypokalaemia and hypercalcaemia.
Gout.
Concomitant use of Atacand Plus and drugs containing aliskiren is contraindicated in patients with diabetes mellitus or impaired renal function (GFR < 60 ml/min/1.73 m^2) (see Sections 4.5 and 5.1).

4.4 Warnings and precautions

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

If double blockade is considered absolutely necessary, this should only be performed under the supervision of a specialist and the patient should be subject to regular, careful 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.

Renal impairment
As with other medicinal products that inhibit the renin-angiotensin-aldosterone system, changes in renal function can be expected in susceptible patients treated with Atacand Plus (see section 4.3).

Kidney transplantation
There is limited clinical data regarding the use of Atacand Plus in patients who have undergone a kidney transplant.

Renal artery stenosis
Drugs that affect the renin-angiotensin-aldosterone system, including angiotensin II receptor antagonists (AIIRA), can raise urea in the blood and serum creatinine in patients with bilateral kidney artery stenosis or kidney artery stenosis in patients with one remaining kidney.

Intravascular volume loss
In patients with intravascular volume and/or sodium loss, symptomatic hypotension may occur, as is described for other substances acting via the renin-angiotensin-aldosterone system. Therefore, the use of Atacand Plus is not recommended until this condition has been treated.

Anaesthesia and surgery
Hypotension may occur during anaesthesia and surgery in patients treated with AIIRA because of the blockade of the renin-angiotensin system. In very rare cases, the drop in blood pressure may be so pronounced that it justifies the use of intravenous fluids and/or vasopressors.

Hepatic impairment
Thiazides should be used with caution in patients with impaired liver function or progressive liver disease, as even mild fluctuations in the fluid and electrolyte balance can induce hepatic coma. There is no clinical experience regarding the use of Atacand Plus in patients with impaired liver function.

Aortic and mitral valve stenosis (obstructive hypertrophic cardiomyopathy)
As with other vasodilators, special care should be taken when treating patients with haemodynamically relevant aortic or mitral valve stenosis or who suffer obstructive hypertrophic cardiomyopathy.

Primary hyperaldosteronism
Patients with primary hyperaldosteronism generally do not respond to antihypertensives that work by inhibiting the renin-angiotensin-aldosterone system. Therefore, the use of Atacand Plus in this population is not recommended.

Electrolyte disturbances
Regular monitoring of serum electrolyte levels should be performed at appropriate intervals. Thiazides, including hydrochlorothiazide, can cause fluid or electrolyte disturbances (hypercalcaemia, hypokalaemia, hyponatremia, hypomagnesaemia and hypochloremic alkalosis).

Thiazide diuretics may reduce the excretion of calcium via the urine and cause recurring, slightly increased concentrations of serum calcium. Significant hypercalcaemia may be sign of a concealed hyperparathyroidism. Thiazides should be stopped before testing the parathyroid function.

Hydrochlorothiazide increases dose-dependent secretion of potassium in the urine, which may lead to hypokalaemia. This effect of hydrochlorothiazide appears to be less noticeable when administered in combination with candesartan cilexetil. The risk of hypokalaemia may be increased in patients with liver cirrhosis, in patients with severe diuresis, in patients with an insufficient oral intake of electrolytes and in patients who are being concomitantly treated with corticosteroids or adrenocorticotropic hormone (ACTH).

Treatment with candesartan cilexetil may cause hyperkalaemia, especially in cases of heart failure and/or reduced kidney function. Concomitant treatment with Atacand Plus and ACE inhibitors, aliskiren, potassium-sparing diuretics, potassium supplements, salt substitutes or other drugs that increase serum potassium levels (e.g. heparin sodium and the combination trimethoprim/sulfamethoxazole) may lead to elevated serum potassium. Potassium levels should be monitored if necessary.

Thiazides have been shown to increase the urine secretion of magnesium, which may lead to hypomagnesaemia.

Metabolic and endocrine effects
Treatment with a thiazide diuretic may impair glucose tolerance. Dose adjustment of antidiabetics, including insulin, may be necessary. Latent diabetes mellitus can manifest during thiazide treatment. Thiazide diuretic therapy is associated with elevated cholesterol and triglyceride. However, with the doses contained in Atacand Plus, only minimal effects have been observed. Thiazide diuretics increase serum uric acid concentrations and can trigger gout in patients with a tendency to develop this condition.

Photosensitivity
Cases of photosensitivity reactions have been reported with thiazide diuretics (see Section 4.8). If a photosensitivity reaction occurs, it is recommended that treatment is

discontinued. If it is necessary to resume treatment, it is recommended to protect exposed areas to the sun or to artificial UVA.

Non-melanoma skin cancer

An increased risk of non-melanoma skin cancer (NMSC) [basal cell cancer (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. Photosensitivity effects of HCTZ could act as a possible mechanism for NMSC.

Patients who take HCTZ should be informed of the risk for NMSC and are advised to regularly check for the presence of new lesions on their skin, and immediately report all suspected skin lesions. Patients should be advised to take all possible preventive measures such as limited exposure to sunlight and UV rays and, in the event of exposure, to adopt sufficient protection to minimise the risk of skin cancer. Suspected skin lesions should be examined immediately and the examination should potentially include 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).

Choroidal effusion, *acute myopia* and *narrow-angle* glaucoma
Hydrochlorothiazide, a sulphonamide, may cause an idiosyncratic reaction that results in choroidal effusion with visual field defect, transient myopia and acute narrow-angle glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and usually occur within hours to weeks after initiation of treatment. Untreated acute narrow-angle glaucoma may lead to permanent vision loss. The primary treatment is to discontinue the drug treatment as quickly as possible. Rapid medical or surgical treatment may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute narrow-angle glaucoma may include 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 hydrochlorothiazide intake. At the onset, symptoms include dyspnoea, fever, pulmonary deterioration and hypotension. If diagnosis of ARDS is suspected, Atacand Plus should be withdrawn and appropriate treatment given. Hydrochlorothiazide should not be administered to patients who previously experienced ARDS following hydrochlorothiazide intake.

General
In patients whose [impaired] vascular tone and renal function are mainly due to the activity of the renin-angiotensin-aldosterone system (e.g. patients with severe heart failure or underlying renal disease, including renal artery stenosis) treatment with drugs that affect this system, including AIIRA, is associated with acute hypotension, azotaemia, oliguria or, in rare cases, acute renal failure. As with all antihypertensive drugs, a too-severe drop

in blood pressure in patients with ischaemic heart disease or atherosclerotic cerebrovascular disease may lead to myocardial infarction or stroke.

Hypersensitivity reactions to hydrochlorothiazide can occur in patients with or without a history of allergic reactions or bronchial asthma, but are more likely in patients with a such history.
Exacerbation or activation of systemic lupus erythematosus has been reported with the use of thiazide diuretics.

The antihypertensive effect of Atacand Plus may be potentiated by other antihypertensive drugs.

This drug contains lactose as an excipient. Patients with any of the following rare hereditary conditions should not use this medicinal product: galactose intolerance, total lactase deficiency or glucose-galactose malabsorption.

Pregnancy
Treatment with AIIRA should not be initiated during pregnancy. If continued treatment with AIIRA is not considered absolutely necessary, patients planning pregnancy should switch to alternative antihypertensive treatments where the safety profile is well documented for use during pregnancy. When pregnancy has been confirmed, treatment with AIIRA should be discontinued immediately and, if appropriate, an alternative treatment should be initiated (see Sections 4.3 and 4.6).

4.5 Interaction with other medicinal products and other forms of interaction

Substances that 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.

It can be expected that the potassium-reducing effect of hydrochlorothiazide is potentiated by other drugs associated with potassium loss and hypokalaemia (e.g. other diuretics, laxatives, amphotericin, carbenoxolone, penicillin G-sodium, salicylic acid derivatives, steroids, ACTH).

Concomitant use of Atacand Plus and potassium-sparing diuretics, potassium supplements or salt substitutes or other medicinal products that can raise serum potassium levels (e.g. heparin sodium and the combination trimethoprim/sulfamethoxazole) may lead to increased serum potassium levels. Potassium levels should be monitored as needed (see Section 4.4).

Diuretic-induced hypokalaemia and hypomagnesaemia predispose the potential cardiotoxic effects of digitalis glycosides and antiarrhythmics. Regular monitoring of serum potassium is recommended when Atacand Plus is administered together with such drugs and with the following drugs that can induce torsades de pointes:

- Class IA antiarrhythmic (e.g. quinidine, hydroquinidine, disopyramide)
- Class III antiarrhythmics (e.g. amiodarone, sotalol, dofetilide, ibutilide)
- Certain antipsychotics (e.g. thioridazine, chlorpromazine, levomepromazine, trifluoperazine, cyamemazine, sulpiride, sultopride, amisulpride, tiapride, pimozide, haloperidol, droperiodol)
- Others (e.g. bepridil, cisapride, diphemanil, i.v. erythromycin, halofantrine, ketanserin, mizolastine, pentamidine, sparfloxacin, terphenadine, i.v. vincamine)

Concomitant administration of lithium and ACE inhibitors or hydrochlorothiazide has been reported to cause reversible increases in serum concentration and lithium toxicity. A similar effect has also been reported with AIIRA. The use of candesartan and hydrochlorothiazide together with lithium is not recommended. Close monitoring of serum lithium levels is recommended if this combination proves necessary.

When AIIRA is co-administered with non-steroidal anti-inflammatory drugs (NSAIDs) (i.e. selective COX-2 inhibitors, acetylsalicylic acid (> 3 g/day) and non-selective NSAIDs), a reduction in the antihypertensive effect may occur.

As with ACE inhibitors, concomitant use of AIIRA and NSAID may lead to an increased risk of impaired renal function, including possible acute renal failure and an increase in serum potassium, especially in patients with already diminished renal function. The combination should be given with caution, especially to the elderly. These patients must receive sufficient hydration and monitoring of renal function upon initiation of the combination treatment and regularly thereafter is recommended.

The diuretic, natriuretic and antihypertensive effects of hydrochlorothiazide are reduced by NSAIDs.

Absorption of hydrochlorothiazide is reduced by colestipol and cholestyramine.

The effect of non-depolarizing skeletal muscle relaxants (e.g., tubocurarine) can be enhanced by hydrochlorothiazide.

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

The hyperglycemic effect of beta blockers and diazoxide may be potentiated by thiazides.

Anticholinergic agents (e.g. atropine, biperiden) can work to increase the bioavailability of thiazide diuretics by reducing gastrointestinal motility and gastric emptying rate.

Thiazides may increase the risk of side effects caused by amantadine.

Thiazides can reduce the renal excretion of cytotoxic drugs (e.g., cyclophosphamide, methotrexate) and enhance their myelosuppressive effects.

Postural hypotension may be potentiated by concomitant use of alcohol, barbiturates or anaesthetics.

Treatment with a thiazide diuretic may impair glucose tolerance. Dose adjustment of antidiabetics, including insulin, may be necessary. Metformin should be used with caution due to the risk of lactic acidosis triggered by possible functional renal failure associated with hydrochlorothiazide.

Hydrochlorothiazide may reduce the arterial response to pressor amines (e.g., adrenaline) but not enough to reverse the pressor effect.

Hydrochlorothiazide may increase the risk of acute renal insufficiency, especially in high doses of contrast agents containing iodine.

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

Concomitant treatment with baclofen, amifostine, tricyclic antidepressants or neuroleptics may lead to a potentiation of the antihypertensive effect and may cause hypotension.

Data from clinical trials have shown that the incidence of adverse events such as hypotension, hyperkalaemia and impaired renal function (including acute renal failure) is higher in double blockade of the renin-angiotensin-aldosterone system (RAAS) through the combined use of ACE inhibitors, angiotensin II receptor blockers or aliskiren, compared to the use of a single RAAS inhibitor drug (see Sections 4.3, 4.4 and 5.1).

4.6 Fertility, pregnancy and lactation

Pregnancy

Angiotensin II Receptor Antagonists (AIIRAs):

Angiotensin II receptor antagonists should not be used during the first trimester of pregnancy (see section 4.4 Warnings and precautions for use). The use of AIIRAs is contraindicated during the second and third trimesters of pregnancy (see sections 4.3 Contraindications and 4.4 warnings and precautions for use).

Epidemiological data concerning the risk of foetal damage following the use of ACE inhibitors during the first trimester of pregnancy is not unambiguous: a somewhat increased risk cannot be excluded. No controlled epidemiological data is available for angiotensin II antagonists, but similar risks may exist for this group of drugs. If

continued treatment with angiotensin II antagonists is not considered necessary, patients planning pregnancy should receive alternative treatment where the safety profile is well documented for use during pregnancy. If pregnancy is confirmed, treatment with angiotensin II antagonists should be discontinued immediately and, if appropriate, an alternative treatment should be started.

It is known that treatment with angiotensin II antagonists during the second and third trimesters can induce human foetal toxicity (impaired renal function, oligohydramnosis, skull ossification defects) and neonatal toxicity (renal failure, hypotension, hyperkalaemia). (See also Section 5.3, Preclinical safety information).

If exposure to angiotensin II antagonists has occurred during the second trimester of pregnancy, ultrasound monitoring of renal function and the skull is recommended.

Infants whose mothers have used angiotensin II antagonists should be observed closely for hypotension (see Section 4.3 Contraindications and 4.4 Warnings and precautions for use).

Hydrochlorothiazide:
Clinical data relating to the use of hydrochlorothiazide during the first trimester of pregnancy is particularly limited. Data from 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 such as icterus, electrolyte disturbances and thrombocytopenia.

Hydrochlorothiazide should not be used for gestational oedema, gestational hypertension or preeclampsia due to the risk of reduced plasma volume and placental hypoperfusion without a beneficial effect on the course of the disease. Hydrochlorothiazide should not be used in the event of essential hypertension in pregnant women, except in rare situations where no other treatment is available.

Breastfeeding

Angiotensin II receptor antagonists (AIIRA):
As no information regarding the use of Atacand Plus during breastfeeding is available, Atacand Plus is not recommended, and instead alternative treatments offering a better documented safety profile are preferable during breastfeeding, especially when breastfeeding newborns or premature babies.

Hydrochlorothiazide:
Hydrochlorothiazide is excreted in human breast milk in small amounts. Thiazides in high doses that cause intensive diuresis can inhibit milk production. The use of Atacand Plus during breastfeeding is not recommended.

4.7 Effects on ability to drive and use machinery

No studies on the effects on ability to drive and use machinery have been performed. Dizziness or tiredness may sometimes occur during treatment with Atacand Plus, which should be considered when driving vehicles or using machinery.

4.8 Undesirable effects

In controlled clinical studies with candesartan cilexetil/hydrochlorothiazide, the observed side effects were mild and transient. The proportion of patients who discontinued treatment due to side effects were the same for candesartan cilexetil/hydrochlorothiazide (2.3-3.3%) and for placebo (2.7-4.3%).

In clinical studies of candesartan cilexetil/hydrochlorothiazide, the observed side effects were limited to those previously reported with candesartan cilexetil and/or hydrochlorothiazide.

The table below shows the side effects of candesartan cilexetil as observed in clinical studies and from experience following market approval. In a pooled analysis of data from clinical studies on patients with hypertension, the determination of the side effects from candesartan cilexetil was based on an incidence of side effects with candesartan cilexetil that was at least 1% higher than the incidence seen with placebo.

The frequencies used throughout the tables in Section 4.8 are: very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1,000, <1/100), rare (≥1/10,000, <1/1,000), very rare (<1/10,000) and no known frequency (cannot be calculated from available data).

System organ class	Frequency	Side 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, hyponatremia
Central and peripheral nervous system disorders	Common	Dizziness/vertigo, headache
Respiratory, thoracic and mediastinal disorders	Very rare	Cough
Gastrointestinal disorders	Very rare	Nausea
	Frequency unknown	Diarrhoea
Hepatobiliary disorders	Very rare	Elevated liver enzymes, abnormal liver function or hepatitis

System organ class	Frequency	Side effect
Skin and subcutaneous tissue disorders	Very rare	Angioedema, skin rash, urticaria, itching
Musculoskeletal and connective tissue disorders	Very rare	Back pain, arthralgia, myalgia
Renal and urinary disorders	Very rare	Reduced renal function, including renal failure in predisposed patients (see Section 4.4)

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

System organ class	Frequency	Side effect
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Frequency unknown	Non-melanoma skin cancer (basal cell cancer and squamous cell carcinoma)
Blood and lymphatic system disorders	Rare	Leuckpenia, neutropenia/agranulocytosis, thrombocytopenia, aplastic anaemia, bone marrow depression, haemolytic anaemia
Immune system	Rare	Anaphylactic reactions
Metabolism and nutrition disorders	Common	Hyperglycaemia, hyperuricaemia, electrolyte disturbances (including hyponatremia and hypokalaemia)
Psychiatric disorders	Rare	Sleep disturbances, depression, restlessness
Central and peripheral nervous system disorders	Common	Dizziness, vertigo
	Rare	Paraesthesia
Eye disorders	Rare	Transient blurred vision
	Frequency unknown	Acute myopia, acute narrow-angle-glaucoma, choroidal effusion
Cardiac disorders	Rare	Cardiac arrhythmias
Vascular disorders	Uncommon	Postural hypotension

System organ class	Frequency	Side effect
	Rare	Necrotising angiitis (vasculitis, cutaneous vasculitis)
Respiratory, thoracic and mediastinal disorders	Rare	Breathing difficulties (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	Icterus (intrahepatic cholestatic icterus)
Skin and subcutaneous tissue disorders	Uncommon	Skin rash, urticaria, photosensitivity reactions
	Rare	Toxic epidermal necrolysis
	Frequency unknown	Systemic lupus erythematosus cutaneous lupus erythematosus
Musculoskeletal and connective tissue disorders	Rare	Muscle spasm
Renal and urinary disorders	Common	Glucosuria
	Rare	Renal dysfunction and interstitial nephritis
General disorders and administration site conditions	Common	Weakness
	Rare	Fever
Examinations	Common	Elevated cholesterol and triglyceride values
	Rare	Elevated BUN and serum creatinine values

Description of selected side effects
Non-melanoma skin cancer: Based on available data from epidemiological studies, a cumulative dose-dependent correlation has been observed between HCTZ and NMSC (see also Sections 4.4 and 5.1).

Reporting of suspected side effects
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form:
https://sideeffects.health.gov.il

4.9 Overdose

Symptoms
With reference to the pharmacological properties, an overdose of candesartan cilexetil is likely to cause mainly symptomatic hypotension and dizziness. In the individual case reports from overdoses (of up to 672 mg of candesartan cilexetil), the patient recovered without complications.

The main effect of hydrochlorothiazide overdose is acute fluid and electrolyte loss. Symptoms such as dizziness, hypotension, thirst, tachycardia, ventricular arrhythmias, sedation/impaired level of consciousness and muscle cramps may also occur.

Treatment

There is no specific information available on the treatment of overdose of Atacand Plus. However, the following measures are suggested in the event of overdose.

If necessary, vomiting should be induced or gastric lavage should be considered. If symptomatic hypotension occurs, symptomatic treatment and the monitoring of vital functions should be initiated. The patient should lie on his/her back with the legs elevated. If this is not sufficient, increase the plasma volume by infusion of an isotonic saline solution. Serum electrolytes and acid-base balance should be checked and corrected if necessary. If the measures mentioned above are not sufficient, sympathomimetics may be administered

Candesartan cannot be eliminated by haemodialysis. It is not known to what extent hydrochlorothiazide is eliminated 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 in the renin-angiotensin-aldosterone system and plays a role in the pathophysiology of hypertension and other cardiovascular diseases. It also plays a role in the pathogenesis behind organ hypertrophy and target organ damage. The main 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 receptor (AT_1 receptor).

Pharmacodynamic effects
Candesartan cilexetil is a prodrug that rapidly converts to the active drug, candesartan, through esterhydrolysis during the absorption from the gastrointestinal tract. Candesartan is an AIIRA and binds selectively to AT_1 receptors. The binding is strong and dissociation from the receptor occurs slowly. Candesartan has no agonist activity.

Candesartan does not affect ACE or other enzyme systems commonly associated with the use of ACE inhibitors. As there is no effect on the breakdown of quinines or on the metabolism of other substances, such as substance P, it is unlikely that AIIRA would be associated with cough. In controlled clinical studies in which candesartan cilexetil was compared with ACE inhibitors, the incidence of cough was lower in patients who received candesartan cilexetil. Candesartan does not bind to or block other hormone receptors or ion channels known to be significant to cardiovascular regulation. The antagonistic effect on AT_1 receptors leads to dose-related increases of the plasma levels of renin, angiotensin I and angiotensin II and a decrease of the plasma concentration of aldosterone.

Non-melanoma skin cancer:

Based on available data from epidemiological studies, a cumulative dose-dependent correlation has been observed between HCTZ and NMSC. A study including a population that consisted of 71,533 cases of BCC and 8,629 cases of SCC matched against 1,430,833 and 172,462 population controls, respectively. High use of HCTZ (≥ 50,000 mg cumulative) was associated with an adjusted odds ratio 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 seen for both BCC and SCC. Another study showed a possible connection 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 odds ratio of 2.1 (95% CI: 1.7-2.6), increasing to an odds ratio of 3.9 (3.0-4.9) for high use (~25,000 mg) and an odds ratio of 7.7 (5.7-10.5) for the highest cumulative dose (~100,000 mg) (see also Section 4.4).

Clinical efficacy and safety

The effects of candesartan cilexetil 8-16 mg (mean dose 12 mg) once daily on cardiovascular morbidity and mortality was evaluated in a randomised clinical study involving 4,937 elderly patients (between 70-89 years of age, 21% were at least 80 years old) with mild to moderate hypertension, who were followed for an average of 3.7 years (Study on Cognition and Prognosis in the Elderly). The patients received candesartan or placebo with the addition of other antihypertensive treatment 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 of major cardiovascular events (cardiovascular mortality, non-fatal stroke and non-fatal myocardial infarction). There

were 26.7 events per 1,000 patient years in the candesartan group versus 30.0 events per 1,000 patient years in the control group (relative risk 0.89; 95% CI 0.75-1.06; p=0.19).

Hydrochlorothiazide inhibits the active reabsorption of sodium, primarily in the distal renal tubules, and promotes the secretion of sodium, chloride and water. The renal secretion of potassium and magnesium increases in a dose-dependent manner, while calcium is reabsorbed to a greater extent. Hydrochlorothiazide reduces plasma volume and extracellular fluid and lowers cardiac output and blood pressure. During long-term treatment, a reduced peripheral resistance contributes to a lowering of blood pressure.

Large clinical studies have shown that long-term treatment with hydrochlorothiazide reduces the risk of cardiovascular morbidity and mortality.

Candesartan and hydrochlorothiazide have additive antihypertensive effects.

In hypertensive patients, Atacand Plus provides a dose-dependent and long-term decrease in arterial blood pressure without any reflex increase in heart rate. No signs of severe hypotension have been observed following the initial dose, or after discontinuation of treatment. The antihypertensive effect usually occurs within 2 hours after a single dose of candesartan cilexetil. With continuous treatment, the majority of the blood pressure decrease is achieved within four weeks and maintained during long-term treatment. Atacand Plus administered once daily provides an effective and consistent blood pressure decrease over 24 hours, and the difference between the highest and lowest effect during the dose interval is small. In a double-blind randomised study, Atacand Plus 16 mg/12.5 mg once daily lowered blood pressure significantly more, and maintained consistent blood pressure for significantly more patients than the combination of losartan/hydrochlorothiazide 50 mg/12.5 mg once daily.

In double-blind randomised studies, the incidence of adverse events, especially cough, was lower in treatment with Atacand Plus than in treatment with combinations of ACE inhibitors and hydrochlorothiazide.

In two clinical studies (randomised, double-blind, placebo-controlled, parallel-group studies) comprising 275 and 1,524 randomised patients**,** respectively, the candesartan cilexetil/hydrochlorothiazide combinations 32 mg/12.5 mg and 32 mg/25 mg provided blood pressure reductions of 22/15 mmHg and 21/14 mmHg, respectively, and were significantly more effective than the corresponding components in monotherapy.
In a randomised, double-blind clinical parallel group study comprising 1975 randomised patients, who could not be optimally controlled with 32 mg candesartan cilexetil once daily, the addition of 12.5 mg or 25 mg hydrochlorothiazide led to further blood pressure reductions. The combination candesartan cilexetil/hydrochlorothiazide 32 mg/25 mg was significantly more effective than the combination 32 mg/12.5 mg, and the overall mean blood pressure reductions were 16/10 mmHg and 13/9 mmHg, respectively.
Candesartan cilexetil/hydrochlorothiazide is equally effective in patients regardless of age and gender.

There is currently no data on the use of candesartan cilexetil/hydrochlorothiazide in patients with kidney disease/nephropathy, reduced left ventricular function/heart failure or in patients who have suffered a 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 Nephropathy in Diabetes) have investigated the combined use of an ACE inhibitor and an angiotensin II receptor blocker.

ONTARGET was a study conducted on patients with a history of cardiovascular and cerebrovascular disease, or type 2 diabetes mellitus accompanied by evidence of final organ damage. VA NEPHRON-D was a study involving patients suffering type 2 diabetes mellitus and diabetes nephropathy.
These studies have shown no significant benefit to renal and/or cardiovascular results and mortality, while an increased risk of hyperkalaemia, acute kidney damage and/or hypotension was observed, as compared with monotherapy. Since their pharmacodynamic properties are similar to each other, 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 benefits of adding aliskiren to a standard treatment with an ACE inhibitor or an angiotensin II receptor blocker in patients with type 2 diabetes mellitus and chronic kidney disease or cardiovascular disease, or both. The study was terminated prematurely because there was an observed increased risk of unwanted outcomes. Both cardiovascular death and stroke were numerically more common in the aliskiren group than in the placebo group and adverse events and serious adverse events of interest (hyperkalaemia, hypotension and renal dysfunction) were reported with a higher frequency in the aliskiren group than in the placebo group.

5.2 Pharmacokinetic properties

Concomitant administration of candesartan cilexetil and hydrochlorothiazide has no clinically significant effect on the pharmacokinetics of any of the substances.

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% for an oral solution of candesartan cilexetil. The relative bioavailability of a tablet formulation of candesartan cilexetil compared to the same oral solution is approximately 34% with very little variability. The mean value for the maximum concentration in serum (C_{max}) is reached 3-4 hours after taking the tablet. Serum candesartan concentrations increase linearly with

increasing doses within the therapeutic dose range. No gender-related differences in the pharmacokinetics of candesartan have been observed. The area below the curve for serum concentration as a function of the time (AUC) for candesartan is not significantly affected by food.

Candesartan binds to a high degree to plasma proteins (to more than 99%). The apparent volume of distribution for 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 absorption by about 15%. The bioavailability may decrease in patients with heart failure and pronounced oedema.

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

Metabolism *and elimination*

Candesartan cilexetil
Candesartan is mainly eliminated unchanged via urine and bile and is only eliminated to a lesser extent by metabolism in the liver (CYP2C9). Available interaction studies do not indicate any effect on CYP2C9 and CYP3A4. Based on *in vitro* data, no interaction is expected to occur *in vivo* with drugs whose metabolism is dependent on cytochrome P450 isoenzymes CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1 or CYP3A4. The terminal half-life ($t_{½}$) for candesartan is approximately 9 hours. No accumulation after repeated dosing has been observed. The half-life of candesartan remains unchanged (approximately 9 hours) after administration of candesartan cilexetil in combination with hydrochlorothiazide. No further accumulation of candesartan occurs after repeated doses of the combination compared to monotherapy.

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

Hydrochlorothiazide
Hydrochlorothiazide is not metabolised and is almost completely excreted as an unchanged substance through glomerular filtration and active tubular secretion. The terminal half-life 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 hours) after administration of hydrochlorothiazide in combination with candesartan cilexetil. No further accumulation of hydrochlorothiazide occurs after repeated doses of the combination compared with monotherapy.

Pharmacokinetics for special groups

Candesartan cilexetil
In elderly people (aged over 65 years), C_{max} and AUC for candesartan are increased by approximately 50% and 80%, respectively, compared to young people. However, the blood pressure response and the incidence of adverse effects are comparable in young and elderly patients after a dose of Atacand Plus (see Section 4.2).

In patients with mild to moderate renal impairment, C_{max} and AUC for candesartan increased with repeated doses by approximately 50% and 70%, respectively, but the terminal half-life did not change, compared to patients with normal renal function. The corresponding change in patients with severe renal impairment was approximately 50% and 110%, respectively. The terminal half-life of candesartan was approximately doubled in patients with severe renal impairment. The pharmacokinetics in patients treated with hemodialysis was comparable to that of patients with severe renal impairment.

In two studies, both of which included patients with mild to moderately impaired liver function, an increase in the mean AUC for candesartan of approximately 20% was observed in one study and 80% in the other study (see Section 4.2). There is no experience from patients with severe hepatic impairment.

Hydrochlorothiazide
The terminal half-life of hydrochlorothiazide is extended in patients with impaired renal function.

5.3 Preclinical safety data

There were no qualitatively new toxicity findings in the combination as compared to that observed for each individual component. In preclinical safety studies, candesartan in itself had effects on the kidneys and on erythrocyte parameters in high doses in mice, rats, dogs and monkeys. Candesartan caused a reduction of the erythrocyte parameters (erythrocytes, haemoglobin, haematocrit). There was an impact of candesartan on the kidneys (such as regeneration, dilatation and basophilia in the tubuli; elevated plasma concentrations of urea and creatinine) that could be secondary to the blood pressure-reducing effect, leading to changes in renal perfusion. The addition of hydrochlorothiazide potentiates the renal toxic effect of candesartan. In addition, candesartan induced hyperplasia/hypertrophy of the juxtaglomerular cells. These changes were assessed to be caused by the pharmacological properties of candesartan and were considered to have little clinical relevance.

Foetal toxicity has been observed during late pregnancy with candesartan. The addition of hydrochlorothiazide did not significantly affect the outcome in studies on foetal development in rats, mice and rabbits (see Section 4.6).

Both candesartan and hydrochlorothiazide show genotoxic activity at very high concentrations/doses. Data from genotoxic studies in vitro and in vivo indicate that it is unlikely that candesartan and hydrochlorothiazide have mutagenic or clastogenic effects in clinical use.

There is no data to indicate that any of the substances are carcinogenic.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Maize starch
Calcium carboxymethylcellulose
Hydroxypropyl cellulose
Polyethylene glycol 8000
Magnesium stearate
Iron oxide yellow CI77492
Iron oxide reddish-brown CI77491

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date is indicated on the packaging materials.

6.4 Special precautions for storage

Store below 30ºC.

6.5 Presentation

16 mg/12.5 mg tablet: PVC/PVDC/al blister packs (Packs of 7, 28 tablets)

6.6 Special precautions for disposal and other handling

No special requirements.

7. REGISTRATION NUMBER

121 44 30145 00.

8. MANUFACTURER

CHEPLAPHARM Arzneimittel GmbH
Ziegelhof 24
17489 Greifswald
Germany

9. LICENSE HOLDER

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Kiryat Matalon
Petah-Tikva

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