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ATACAND PLUS® 16/12.5 mg

candesartan cilexetil and hydrochlorothiazide
Tablet

Fertility, Pregnancy and Lactation
Use in pregnancy
The use of Atacand Plus is contraindicated during pregnancy (see 'Contraindications'). Patients receiving Atacand Plus should be made aware of that before contemplating a possibility of becoming pregnant so that they can discuss appropriate options with their treating physician. When pregnancy is diagnosed, treatment with Atacand Plus must be stopped immediately and if appropriate, alternative therapy should be started.

When used in pregnancy, drugs that act directly on the renin-angiotensin system can cause foetal and neonatal injury and death. Exposure to angiotensin II receptor antagonist therapy is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia) (see 'Preclinical safety data').

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 pregnancy may compromise foeto-placental perfusion and may cause foetal and neonatal effects like icterus, disturbance of electrolyte balance and thrombocytopenia.

Use in lactation
It is not known whether candesartan is excreted in human milk. However, candesartan is excreted in the milk of lactating rats. Hydrochlorothiazide passes into mother's milk.

Because of the potential for adverse effects on the nursing infant, breast feeding should be discontinued if the use of Atacand Plus is considered essential (see 'Contraindications').

Composition
One tablet contains 16 mg candesartan cilexetil and 12.5 mg hydrochlorothiazide.

Pharmaceutical Form
Tablets.

Atacand Plus 16 mg/12.5 mg are peach, oval, biconvex tablets with a score on both sides and engraved A/CS.

Therapeutic Indications
Hypertension, where a monotherapy is not sufficiently effective.

Posology and method of administration
Dosage in Hypertension
The recommended dose of Atacand Plus is 1 tablet once daily.

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

When clinically appropriate a direct change from monotherapy to Atacand Plus may be considered. Dose titration of candesartan cilexetil is recommended when switching from hydrochlorothiazide monotherapy.

Administration
Atacand Plus should be taken once daily with or without food.

Use in the elderly
No dosage adjustment is necessary in elderly patients.

Use in impaired renal function
In patients with mild to moderate renal impairment (i.e., creatinine clearance between 30-80 ml/min/1.73m^2 BSA), a dose titration is recommended.

Atacand Plus should not be used in patients with severe renal impairment (creatinine clearance <30 ml/min/1.73 m^2 BSA).

Use in impaired hepatic function
Patients with hepatic impairment: Dose titration is recommended in patients with mild to moderate chronic liver disease.

Atacand Plus should not be used in patients with severe hepatic impairment and/or cholestasis.

Use in children
The safety and efficacy of Atacand Plus have not been established in children.

Contraindications
Hypersensitivity to any component of Atacand Plus or to sulfonamide derived drugs (hydrochlorothiazide is a sulfonamide derived drug).

Pregnancy and lactation (see 'Fertility, pregnancy and lactation').

Severe renal impairment (creatinine clearance <30 ml/min/1.73 m^2 BSA).

Severe hepatic impairment and/or cholestasis.

Gout.

The use of candesartan cilexetil in combination with aliskiren-containing medicines in patients with diabetes mellitus (type I or II) or with moderate to severe renal impairment (GFR <60 ml/min/1.73m^2).

Special warnings and special precautions for use
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 'Interaction with other medicinal products and other forms of interaction').

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.

The use of candesartan cilexetil with aliskiren is contraindicated in patients with diabetes mellitus (type I or II) or moderate to severe renal impairment (GFR <60 ml/min/1.73m^2) (see 'Contraindications').

Renal artery stenosis
Other drugs that affect the renin-angiotensin-aldosterone system, i.e. angiotensin converting enzyme (ACE) inhibitors, may increase blood urea and serum creatinine in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney. A similar effect may be anticipated with angiotensin II receptor antagonists.

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 Atacand Plus is not recommended until this condition has been corrected.

Anaesthesia and surgery
Hypotension may occur during anaesthesia and surgery in patients treated with angiotensin II antagonists due to blockade of the renin-angiotensin system. Very rarely, hypotension may be severe such that it may warrant the use of intravenous fluids and/or vasopressors.

Renal impairment
As with other agents inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible patients treated with Atacand Plus (see 'Contraindications').

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 exposure has been observed in two epidemiological studies based on the Danish National Cancer Registry. Photosensitizing actions of hydrochlorothiazide could act as a possible mechanism for NMSC.

Patients taking hydrochlorothiazide should be informed on 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 hydrochlorothiazide may also need to be reconsidered in patients who have experienced previous NMSC.

Acute respiratory toxicity
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 cilexetil/hydrochlorothiazide should be withdrawn, and appropriate treatment given. Hydrochlorothiazide should not be administered to patients who previously experienced ARDS following hydrochlorothiazide intake.

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

Aortic and mitral valve stenosis or 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.

Electrolyte imbalance
As for any patient receiving diuretic therapy, 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).

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.

Based on experience with the use of other drugs that affect the renin-angiotensin-aldosterone system, concomitant use of Atacand Plus and ACE inhibitors, aliskiren, potassium-sparing diuretics, potassium supplements or salt substitutes or other drugs that may increase serum potassium levels (e.g. heparin, co-trimoxazole) may lead to increases in serum potassium.

Metabolic and endocrine effects
Treatment with a thiazide diuretic may impair glucose tolerance. Dosage adjustment of antidiabetic drugs, 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. However, at the 12.5 mg dose contained in Atacand Plus minimal or no effects were reported. Thiazide diuretics increase serum uric acid concentration and may precipitate gout in susceptible patients.

Choroidal effusion, Acute Myopia and 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.

General
In patients whose vascular tone and renal function depend predominantly on the activity of the renin-angiotensin-aldosterone system (e.g. patients with severe congestive heart failure or underlying renal disease, including renal artery stenosis), treatment with other drugs that affect this system has been associated with acute hypotension, azotaemia, oliguria or, rarely, acute renal failure. As with any antihypertensive agent, excessive blood pressure decrease in patients with ischaemic heart disease or atherosclerotic cerebrovascular disease could result in a myocardial infarction or stroke.

Interaction with other medicinal products and other forms of interaction
Clinical trial data has shown that dual blockade of the 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 'Contraindications' and 'Special warnings and special precautions for use')

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

The bioavailability of candesartan is not affected by food.

The antihypertensive effect of Atacand Plus may be enhanced by other antihypertensives.

The potassium depleting effect of hydrochlorothiazide could be expected to be potentiated by other drugs associated with potassium loss and hypokalaemia (e.g. other kaliuretic diuretics, laxatives, amphotericin, carbenoxolone, salicylic acid derivatives).

Diuretic-induced hypokalaemia and hypomagnesaemia predisposes to the potential cardiotoxic effects of digitalis glycosides and antiarrhythmics. Periodic monitoring of serum potassium is recommended when Atacand Plus is administered with such drugs.

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors or hydrochlorothiazide. A similar effect may occur with angiotensin II receptor antagonists (AIIRAs) and careful monitoring of serum lithium levels is recommended during concomitant use.

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

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

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

The absorption of hydrochlorothiazide is reduced by colestipol or cholestyramine.

Thiazides may increase the responsiveness to nondepolarizing skeletal muscle relaxants (e.g. tubucurarine).

Treatment with a thiazide diuretic may impair glucose tolerance. Other antidiabetic drugs including insulin requirements in diabetic patients may be increased, decreased, or unchanged.

Thiazides may decrease arterial responsiveness to noradrenaline, but not enough to preclude effectiveness of the pressor agent for therapeutic use.

Hypokalemia may develop during concomitant use of steroids or adrenocorticotropic hormone (ACTH).

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 diazoxide may be enhanced by thiazides.

Thiazides 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.

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

There is no clinically significant interaction between hydrochlorothiazide and food.

Effects on ability to drive and use machines
The effect of Atacand Plus on the ability to drive and use machines has not been studied, but based on its pharmacodynamic properties Atacand Plus is unlikely to affect this ability. When driving vehicles or operating machines, it should be taken into account that occasionally dizziness or weariness may occur during treatment of hypertension.

Undesirable effects
Adverse events were mild and transient and comparable to placebo in controlled clinical studies with various doses of candesartan cilexetil/hydrochlorothiazide (candesartan cilexetil up to 32 mg and hydrochlorothiazide up to 25 mg). The overall incidence of adverse events showed no association with age or gender.

Withdrawals from treatment due to adverse events were similar with candesartan cilexetil/hydrochlorothiazide (2.3 - 3.3%) and placebo (2.7 - 4.3%).

Candesartan cilexetil
The following adverse reactions have been reported very rarely (<1/10,000) with candesartan cilexetil in post marketing experience.

Blood and lymphatic system disorders:
Leukopenia, neutropenia and agranulocytosis

Metabolism and nutrition disorders:
Hyperkalaemia, hyponatraemia

Nervous system disorders:
Dizziness

Respiratory, thoracic and mediastinal disorders:
Cough

Hepato-biliary disorders:
Increased liver enzymes, abnormal hepatic function or hepatitis

Skin and subcutaneous tissue disorders:
Angioedema, rash, urticaria, pruritus

Musculoskeletal, connective tissue and bone disorders:
Back pain

Renal and urinary disorders:
Renal impairment, including renal failure in susceptible patients (see 'Special warnings and special precautions for use').

Code-Leserichtung

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Hydrochlorothiazide
The following adverse reactions have been reported with hydrochlorothiazide monotherapy, usually with doses of 25 mg or greater. The frequencies used are: Uncommon (>1/1000 and <1/100), rare (<1/1000) and not known (cannot be estimated from the available data).

Blood and lymphatic system disorders:
Rare: Leukopenia, neutropenia/agranulocytosis, thrombocytopenia, aplastic anaemia, haemolytic anaemia

Immune system disorders:
Rare: Anaphylactic reactions

Eye disorders:
Not known: Choroidal effusion, acute myopia, acute angle-closure glaucoma

Vascular disorders:
Uncommon: Postural hypotension
Rare: Necrotising angitis (vasculitis)

Respiratory, thoracic and mediastinal disorders:
Rare: Respiratory distress (including pneumonitis, pulmonary oedema and acute respiratory distress syndrome)

Gastrointestinal disorders:
Rare: Pancreatitis

Hepatobiliary disorders:
Rare: Jaundice (intrahepatic cholestatic jaundice)

Skin and subcutaneous tissue disorders:
Uncommon: Photosensitivity reactions
Rare: Toxic epidermal necrolysis
Frequency unknown: Systemic lupus erythematosus, cutaneous lupus erythematosus

Renal and urinary disorders:
Rare: Renal dysfunction and interstitial nephritis

Neoplasms benign, malignant and unspecified (incl cysts and polyps)
Frequency unknown: Non-melanoma skin cancer (Basal cell carcinoma and Squamous cell carcinoma)

Laboratory findings
In general, there were no clinically important influences of candesartan cilexetil/hydrochlorothiazide on routine laboratory variables. Increases in serum uric acid, blood glucose and serum ALAT (SGPT) were reported as adverse events slightly more often with candesartan cilexetil/hydrochlorothiazide (crude rates 1.1%, 1.0% and 0.9%, respectively) than with placebo (0.4%, 0.2% and 0%, respectively). Minor decreases in haemoglobin and increases in serum ASAT (SGOT) have been observed in single patients receiving candesartan cilexetil/hydrochlorothiazide. Increases in creatinine, urea or potassium and decrease in sodium have been observed.

Description of selected adverse reactions
Non-melanoma skin cancer
Based on available data from epidemiological studies, cumulative dose-dependent association between hydrochlorothiazide and NMSC has been observed.

Overdose
Symptoms
Based on pharmacological considerations, the main manifestation of an overdose of candesartan cilexetil is likely to be symptomatic hypotension and dizziness. In single case reports of overdose (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 overdosage with Atacand Plus. 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 drugs 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.

Pharmacodynamic properties
Pharmaco-therapeutic group: Angiotensin II antagonists + diuretics, ATC code C09DA06.

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 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.

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 angiotensin II receptor antagonist, 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, angiotensin II receptor antagonists 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.

In the SCOPE (Study on COgnition and Prognosis in the Elderly) trial, the effects of candesartan cilexetil based antihypertensive treatment on cardiovascular morbidity and mortality, cognitive function and quality of life were assessed in 4,937 elderly patients (aged 70-89 years) with hypertension (SBP 160-179 mmHg and/or DBP 90-99 mmHg). The table shows the study results for the primary endpoint (major cardiovascular events) and its components. Both treatment regimens lowered systolic and diastolic blood pressure effectively and were generally well tolerated. Cognitive function and quality of life were well maintained in both treatment arms.

	No. of patients with a first event			
	Candesartan cilexetil* (N=2477)	**Control* (N=2460)**	**Relative risk (95% CI)**	**p-value**
Major CV events	242	268	0.89 (0.75-1.06)	0.19
- CV 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 standardized to hydrochlorothiazide 12.5 mg once daily before randomisation. Other antihypertensive treatment was added to the double-blind study medication (candesartan cilexetil 8-16 mg or corresponding placebo once daily) if SBP remained ≥ 160 mmHg and/or DBP ≥ 90 mmHg. Such add-on treatment was given to 49% and 66% of the patients in the candesartan cilexetil and control groups, respectively.

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, Atacand Plus results 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 Atacand Plus, 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. Atacand Plus once daily provides effective and smooth blood pressure reduction over 24 hours, with little difference between peak and trough effects during the dosing interval. In a double-blind randomised study, Atacand Plus 16 mg/12.5 mg once daily reduced blood pressure significantly more, and controlled the blood pressure of significantly more patients, than the losartan/hydrochlorothiazide combination 50 mg/12.5 mg once daily.

In double-blind, randomised studies, the incidence of adverse events, especially cough, was lower during treatment with Atacand Plus 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 adequately 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.

Non-melanoma skin cancer: Based on available data from epidemiological studies, cumulative dose-dependent association between hydrochlorothiazide 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 hydrochlorothiazide 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 hydrochlorothiazide: 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).

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 drug 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.

Metabolism 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 interactions studies indicate no effect on CYP2C9 and CYP3A4.

Based on *in vitro* data, no interaction would be expected to occur *in vivo* with drugs 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. There is a slight clinically nonsignificant increase in AUC and C_{max} of candesartan when given together with hydrochlorothiazide. No 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 metabolized 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 Atacand Plus in young and elderly patients (see 'Dosage and method of administration').

In patients with mild to moderate renal impairment, C_{max} and AUC of candesartan increased during repeated dosing by approximately 50% and 70%, respectively, but 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 patients with mild to moderate hepatic impairment, there was an increase in the AUC of candesartan of approximately 20%. In patients with moderate to severe hepatic impairment, the increase in the AUC of candesartan was approximately 80%.

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

Preclinical safety data
In a variety of preclinical studies conducted in several species, expected exaggerated pharmacological effects of both compounds have been seen. The kidney is the main target organ. Addition of hydrochlorothiazide caused a slight potentiation of the nephrotoxicity seen with candesartan alone, however, without any qualitatively new findings. Animal studies with candesartan cilexetil have demonstrated late foetal and neonatal injury in the kidney. The mechanism is believed to be pharmacologically mediated through effects on the renin-angiotensin-aldosterone system.

The late foetal effects seen with candesartan was not potentiated by the combination treatment.

There was no evidence of mutagenicity or clastogenicity at clinically relevant levels and there was no indication that either compound is carcinogenic.

List of excipients
16/12.5 mg: carmellose calcium, hydroxypropyl cellulose, lactose, magnesium stearate, maize starch, polyethylene glycol, iron oxide yellow (E172) and iron oxide red (E172).

Shelf life
Please refer to expiry date on the outer carton.

Pack size
16/12.5 mg: 30 tablets.

Special precautions for storage
Store below 30°C.

Manufacturer
Klocke Pharma-Service GmbH, 77767 Appenweier, Germany

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