ATACAND® PLUS
(candesartan cilexetil/hydrochlorothiazide)

Fertility, pregnancy and lactation

Use in pregnancy
The use of Atacand Plus is contraindicated during pregnancy (see section 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 section 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, Atacand Plus should not be given during breast-feeding (see section Contraindications).

1. NAME OF THE MEDICINAL PRODUCT

Atacand® Plus 16/12.5 mg
candesartan cilexetil/hydrochlorothiazide
tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One Atacand Plus tablet contains 16 mg candesartan cilexetil and 12.5 mg hydrochlorothiazide. For excipients (see section List of excipients).

3. 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 on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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.

The dose of candesartan cilexetil should be titrated before switching to Atacand Plus.

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 patients with intravascular volume depletion

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

Use in impaired renal function

In patients with mild to moderate renal impairment (ie, creatinine clearance between 30-80 ml/min/1.73 m^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.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients or to sulfonamide derived drugs (hydrochlorothiazide is a sulfonamide derived drug) or to any of the excipients.

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

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

Severe hepatic impairment and/or cholestasis.

Refractory hypokalaemia and hypercalcaemia.

Gout.

The concomitant use of Atacand Plus with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m^2) (see section Interaction with other medicinal products and other form of interaction).

4.4 Special warnings and precautions for use

Renal impairment

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

Kidney transplantation

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

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 section Interaction with other medicinal products and other form of interaction).

If dual blockade therapy is considered 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.

Concomitant use of aliskiren with angiotensin II receptor blockers (ARBs) and angiotensin-converting enzyme (ACE) inhibitors is contraindicated in patients with diabetes mellitus (type I or II) or moderate to severe renal impairment (GFR < 60 ml/min/1.73 m^2) (see section Contraindications and Interaction with other medicinal products and other form of interaction).

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.

Non-melanoma skin cancer

A potential association of non-melanoma skin cancer (NMSC) [basal cell carcinoma (BCC) and squamous cell carcinoma (SCC)] with increasing cumulative dose of hydrochlorothiazide (HCTZ) exposure has been reported in two epidemiological case control studies based on Danish National cancer registry. Photosensitizing actions of HCTZ could act as a possible mechanism for NMSC although a causal relationship has not been established.

Patients taking HCTZ should be informed of the association of NMSC with HCTZ use 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 adequate protection, when exposed to sunlight, should be advised to the patients in order to minimize the risk of skin cancer. Suspicious skin lesions should be promptly examined potentially including histological examinations of biopsies. The use of HCTZ may also need to be reconsidered in patients who have experienced previous NMSC.

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.

Hepatic impairment

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

Aortic and mitral valve stenosis (obstructive hypertrophic cardiomyopathy)

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

Primary hyperaldosteronism

Patients with primary hyperaldosteronism generally will not respond to antihypertensive drugs acting through inhibition of the renin-angiotensin-aldosterone system. Therefore the use of Atacand Plus is not recommended.

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).

Thiazide diuretics may decrease the urinary calcium excretion and may cause intermittent and

slightly increased serum calcium concentrations.

Marked hypercalcaemia may be a sign of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

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

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.

Although not documented with Atacand Plus treatment with angiotensin converting enzyme inhibitors or angiotensin II receptor antagonists may cause hyperkalaemia, especially in the presence of heart failure and/or renal impairment.

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

Metabolic and endocrine effects

Treatment with a thiazide diuretic may impair glucose tolerance. 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. The possibility of similar effects cannot be excluded with angiotensin II receptor antagonists. As with any antihypertensive agent, excessive blood pressure decrease in patients with ischaemic heart disease or atherosclerotic cerebrovascular disease could result in a myocardial infarction or stroke.

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

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

4.5 Interaction with other medicinal products and other form 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 section Contraindications and Special warnings and 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, penicillin G sodium, salicylic acid derivatives).

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

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.

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

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

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

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

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

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

The risk for hypokalaemia may be increased during concomitant use of steroids or adrenocorticotropic hormone (ACTH).

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

Treatment with a thiazide diuretic may impair glucose tolerance. Dosage adjustment of antidiabetic drugs, including insulin, may be required.

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

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

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.

4.6 Pregnancy and lactation

Use in pregnancy

The use of Atacand Plus is contraindicated during pregnancy (see section 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 section 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, Atacand Plus should not be given during breast-feeding (see section Contraindications).

4.7 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.

4.8 Undesirable effects

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

In a pooled analysis of clinical trial data, the following common (>1/100) adverse reactions with candesartan cilexetil/hydrochlorothiazide were reported based on an incidence of adverse events with candesartan cilexetil/hydrochlorothiazide at least 1% higher than the incidence seen with placebo:

Nervous system disorders:
Dizziness/vertigo

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

Respiratory, thoracic and mediastinal disorders:
Cough

Nervous system disorders:
Dizziness, headache

Gastrointestinal disorders:
Nausea

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, arthralgia, myalgia

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

Hydrochlorothiazide

The following adverse reactions have been reported with hydrochlorothiazide, usually with doses of 25 mg or greater. The frequencies used are: Common (>1/100), 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: Leucopenia, neutropenia/agranulocytosis, thrombocytopenia, aplastic anaemia, bone marrow depression, haemolytic anaemia

Immune system disorders:
Rare: Anaphylactic reactions

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

Metabolism and nutrition disorders:
Common: Hyperglycaemia, hyperuricaemia, electrolyte imbalance (including hyponatraemia and hypokalaemia)

Psychiatric disorders:
Rare: Sleep disturbances, depression, restlessness

Nervous system disorders:
Common: Light-headedness, vertigo
Rare: Paraesthesia

Eye disorders:
Rare: Transient blurred vision

Cardiac disorders:
Rare: Cardiac arrhythmias

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

Respiratory, thoracic and mediastinal disorders:
Rare: Respiratory distress (including pneumonitis, pulmonary oedema and acute respiratory distress syndrome) (See Section Special warnings and precautions for use)

Gastrointestinal disorders:
Uncommon: Anorexia, loss of appetite, gastric irritation, diarrhoea, constipation
Rare: Pancreatitis

Hepatobiliary disorders:
Rare: Jaundice (intrahepatic cholestatic jaundice)

Skin and subcutaneous tissue disorders:
Uncommon: Rash, urticaria, photosensitivity reactions
Rare: Toxic epidermal necrolysis
Frequency not known: Systemic lupus erythematosus, cutaneous lupus erythematosus

Musculoskeletal and connective tissue disorders:
Rare: Muscle spasm

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

General disorders and administration site conditions:
Common: Weakness
Rare: Fever

Investigations:
Common: Increases in cholesterol and triglycerides
Rare: Increases in BUN and serum creatinine

Laboratory findings

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.

4.9 Overdose

Symptoms

Based on pharmacological considerations, the main manifestation of an overdose of candesartan cilexetil is likely to be symptomatic hypotension and dizziness. In individual case reports of overdose (of up to 672 mg candesartan cilexetil) patient recovery was uneventful.

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

Management

No specific information is available on the treatment of 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 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 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.

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

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

Large clinical studies have shown that long-term treatment with hydrochloro-thiazide reduces the risk for cardiovascular morbidity and mortality.

Candesartan and hydrochlorothiazide have additive antihypertensive effects.

In hypertensive patients, Atacand Plus causes an effective 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 maximum 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 significantly more patients, than an approved similar fixed combination product containing losartan 50 mg and hydrochlorothiazide 12.5 mg. In double-

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

In two clinical studies (randomised, double-blind, placebo controlled, parallel group) including 275 and 1524 randomised patients respectively, the candesartan cilexetil/hydrochlorothiazide combinations 32 mg/12.5 mg and 32 mg/25 mg resulted in blood pressure reductions of 21/14 mmHg for the highest dose, 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.

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

5.2 Pharmacokinetic properties

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

Absorption and distribution

Candesartan cilexetil

Following oral administration, candesartan cilexetil is converted to the active 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 interaction 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 an increase in AUC (15-18%) and C_{max} (23-24%) of candesartan when given together with hydrochlorothiazide. This is of no clinical importance. Furthermore titration of the individual components is recommended before switching to Atacand Plus. No additional accumulation of candesartan occurs after repeated doses of the combination compared to monotherapy.

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

Hydrochlorothiazide

Hydrochlorothiazide is not 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 section Posology 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 a 23% increase in the AUC of

candesartan.

Hydrochlorothiazide

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

Preclinical safety data

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

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

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

There was no evidence that either compound is carcinogenic.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Carmellose calcium, hydroxypropyl cellulose, iron oxide red E172, iron oxide yellow E172, lactose monohydrate, magnesium stearate, maize starch and macrogol.

6.2 Shelf life

Please refer to expiry date on the outer carton.

6.3 Special precautions for storage

Do not store above 30°C.

6.4 Pack size

Please refer to outer carton for pack size.

Product Owner

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