

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Atacand Plus 8/12.5 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One Atacand Plus tablet contains 8 mg candesartan cilexetil and 12.5 mg hydrochlorothiazide.

Each tablet contains 77 mg lactose monohydrate. For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.

Atacand Plus 8/12.5 mg are white, oval, biconvex tablets with a score on both sides and engraved A/CK 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

The recommended dose of Atacand Plus is 8/12.5 mg once daily.

When clinically appropriate a direct change from monotherapy to Atacand Plus may be considered. Most of the antihypertensive effect is usually attained within 4 weeks of initiation of treatment.

Administration

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

Use in the elderly

No initial 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

Loop diuretics are preferred to thiazides in this population. Dose titration of candesartan cilexetil is recommended in patients with renal impairment whose creatinine clearance is ≥ 30 ml/min/1.73 m² BSA before treatment with Atacand Plus (the recommended starting dose of candesartan cilexetil is 4 mg in patients with mild to moderate renal impairment). Atacand Plus should not be used in patients with severe renal impairment (creatinine clearance <30 ml/min/1.73 m² BSA).

Use in impaired hepatic 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 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 Contra-indications

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

Pregnancy and lactation (see section 4.6 Pregnancy and lactation).

Severe renal impairment (creatinine clearance <30 ml/min/1.73 m² BSA).

Severe hepatic impairment and/or cholestasis.

Refractory hypokalaemia and hypercalcaemia.

Gout.

4.4 Special warnings and precautions for use

Renal impairment/kidney transplantation

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Loop diuretics are preferred to thiazides in this population. When Atacand Plus is used in patients with impaired renal function, a periodic monitoring of potassium, creatinine and uric acid levels is recommended.

There is no experience regarding the administration of Atacand Plus in patients with a recent kidney transplantation.

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.

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 aldosteronism generally will not respond to antihypertensive drugs acting through inhibition of the renin-angiotensin 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 hypochloroemic 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 adrenocorticotrophic hormone (ACTH).

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.

Although not documented with Atacand Plus treatment with angiotensin converting enzyme inhibitors or angiotensin-II-receptor inhibitors 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.

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.

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

4.5 Interaction with other medicinal products and other forms of interaction

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

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 and careful monitoring of serum lithium levels is recommended during concomitant use.

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

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

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

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. cyclo-phosphamide, methotrexate) and potentiate their myelosuppressive effects.

The risk for hypokalaemia may be increased during concomitant use of steroids or adrenocorticotrophic 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.

There is no clinically significant interaction between hydrochlorothiazide and food.

4.6 Pregnancy and lactation

Use in pregnancy

There are very limited data from the use of Atacand Plus in pregnant women. These data are insufficient to allow conclusions about potential risk for the foetus when used during the first trimester. In humans, foetal renal perfusion, which is dependent upon the development of the renin-angiotensin-aldosterone system, begins in the second trimester. Thus risk to the foetus increases if Atacand Plus is administered during the second or third trimesters of pregnancy. When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin system can cause foetal and neonatal injury (hypotension, renal dysfunction, oliguria and/or anuria, oligohydramnios, skull hypoplasia, intrauterine growth retardation) and death. Cases of lung hypoplasia, facial abnormalities and limb contractures have also been described.

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.

Hydrochlorothiazide can reduce the plasma volume as well as the uteroplacental blood flow. It may also cause neonatal thrombocytopenia.

Based on the above information, Atacand Plus is contra-indicated in pregnancy. If pregnancy is detected during treatment, Atacand Plus should be discontinued (see section 4.3 Contra-indications).

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 is contra-indicated during breast-feeding (see section 4.3 Contra-indications).

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 (3.3%) and placebo (2.7%).

In a pooled analysis of clinical trial data, the following 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.

The frequencies used in the tables throughout this section are: very common ($\geq 1/10$) common ($\geq 1/100 < 1/10$), uncommon ($\geq 1/1000, < 1/100$), rare ($\geq 1/10\ 000, < 1/1000$) and very rare ($< 1/10\ 000$):

System Organ Class	Frequency	Undesirable Effect
Nervous system disorders	Common	Dizziness/vertigo

The following adverse reactions have been reported with candesartan cilexetil in post marketing experience:

System Organ Class	Frequency	Undesirable Effect
Blood and lymphatic system disorders	Very rare	Leukopenia, neutropenia and agranulocytosis
Metabolism and nutrition disorders	Very rare	Hyperkalaemia, hyponatraemia
Nervous system disorders	Very rare	Dizziness, headache
Gastrointestinal disorders	Very rare	Nausea
Hepatobiliary disorders	Very rare	Increased liver enzymes, abnormal hepatic function or hepatitis
Skin and subcutaneous tissue disorders	Very rare	Angioedema, rash, urticaria, pruritus
Musculoskeletal, connective tissue and bone disorders	Very rare	Back pain, arthralgia, myalgia
Renal and urinary disorders	Very rare	Renal impairment, including renal failure in susceptible patients (see section 4.4)

The following adverse reactions have been reported with hydrochlorothiazide monotherapy, usually with doses of 25 mg or greater:

System Organ Class	Frequency	Undesirable Effect
Blood and lymphatic system disorders	Rare	Leucopenia, neutropenia/agranulocytosis,

System Organ Class	Frequency	Undesirable Effect
		thrombocytopenia, aplastic anaemia, bone marrow depression, haemolytic anaemia
Immune system disorders	Rare	Anaphylactic reactions
Metabolism and nutrition disorders	Common	Hyperglycaemia, hyperuricaemia, electrolyte imbalance (including hyponatraemia and hypokalaemia)
Psychiatric disorders	Rare	Sleep disturbances, depression, restlessness
Nervous system disorders	Common	Light-headedness, vertigo
	Rare	Paraesthesia
Eye disorders	Rare	Transient blurred vision
Cardiac disorders	Rare	Cardiac arrhythmias
Vascular disorders	Uncommon	Postural hypotension
	Rare	Necrotising angiitis (vasculitis, cutaneous vasculitis)
Respiratory, thoracic and mediastinal disorders	Rare	Respiratory distress (including pneumonitis and pulmonary oedema)
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, cutaneous lupus erythematosus-like reactions, reactivation of cutaneous lupus erythematosus
Musculoskeletal, connective tissue and bone 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

System Organ Class	Frequency	Undesirable Effect
	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 can not 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 C09D A.

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 (AT₁) 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 AT₁ 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 AT₁ 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 hydrochlorothiazide 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 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.

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

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 ($t_{1/2}$) 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 (see section 4.2). 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 $t_{1/2}$ 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 4.2 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 $t_{1/2}$ 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 $t_{1/2}$ 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 $t_{1/2}$ of hydrochlorothiazide is prolonged in patients with renal impairment.

5.3 Preclinical safety data

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

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

There was no evidence that either compound is carcinogenic.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Carmellose calcium
Hydroxypropylcellulose
Lactose monohydrate
Magnesium stearate
Maize starch
Macrogol

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

3 years.

6.4 Special precautions for storage

No special precautions for storage.

6.5 Nature and contents of container

8 mg/12.5 mg tablet: PVC/PVDC blister packs of 7, 14, 15, 28, 30, 50, 56, 98, 98x1 (single dose unit), 100 and 300 tablets.

8 mg/12.5 mg tablet: HDPE bottles of 100 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

To be completed nationally.

8. MARKETING AUTHORISATION NUMBER(S)

To be completed nationally.

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

To be completed nationally.

10. DATE OF REVISION OF THE TEXT

22 October 2008

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