Annex III

Summary of product characteristics, labelling and package leaflet

Note: This SPC, labelling and packages leaflet is the version valid at the time of Commission decision.

After the Commission decision the Member State competent authorities, in liaison with the reference Member State, will update the product information as required. Therefore, this SPC, labelling and package leaflet may not necessarily represent the current text.

Summary of product characteristics

1. NAME OF THE MEDICINAL PRODUCT

Atacand Plus and associated names (see Annex I) 8 mg/12.5 mg tablets
Atacand Plus and associated names (see Annex I) 16 mg/12.5 mg tablets
Atacand Plus and associated names (see Annex I) 32 mg/12.5 mg tablets
Atacand Plus and associated names (see Annex I) 32 mg/25 mg tablets

[See Annex I – To be completed nationally]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

[To be completed nationally]

3. PHARMACEUTICAL FORM

Tablet.

[To be completed nationally]

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Atacand Plus is indicated for the:

- Treatment of essential hypertension in adult patients whose blood pressure is not optimally controlled with candesartan cilexetil or hydrochlorothiazide monotherapy.

4.2 Posology and method of administration

Posology

The recommended dose of Atacand Plus is one tablet once daily.

Dose titration with the individual components (candesartan cilexetil and hydrochlorothiazide) is recommended. When clinically appropriate a direct change from monotherapy to Atacand Plus may be considered. Dose titration of candesartan cilexetil is recommended when switching from hydrochlorothiazide monotherapy. Atacand Plus may be administered in patients whose blood pressure is not optimally controlled with candesartan cilexetil or hydrochlorothiazide monotherapy or Atacand Plus at lower doses.

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

Special populations

Elderly population
No dose adjustment is necessary in elderly patients.

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).

Patients with renal impairment
Loop diuretics are preferred to thiazides in this population. Dose titration of candesartan cilexetil is recommended in patients with mild to moderate renal impairment (creatinine clearance ≥ 30 ml/min/1.73 m^2 Body Surface Area (BSA)) before treatment with Atacand Plus (the recommended starting dose of candesartan cilexetil is 4 mg in these patients).
Atacand Plus is contraindicated in patients with severe renal impairment (creatinine clearance < 30 ml/min/1.73 m^2 BSA) (see section 4.3).

Patients with hepatic impairment
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 4 mg in these patients).
Atacand Plus is contraindicated in patients with severe hepatic impairment and/or cholestasis (see section 4.3).

Paediatric population

The safety and efficacy of Atacand Plus in children aged between birth and 18 years have not been established. No data are available.

Method of administration

Oral use.
Atacand Plus can be taken with or without food.
The bioavailability of candesartan is not affected by food.
There is no clinically significant interaction between hydrochlorothiazide and food.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients or to sulfonamide derived active substances. Hydrochlorothiazide is a sulfonamide derived active substance.
Second and third trimesters of pregnancy (see sections 4.4 and 4.6)
Severe renal impairment (creatinine clearance < 30 ml/min/1.73 m^2 BSA).
Severe hepatic impairment and/or cholestasis.
Refractory hypokalaemia and hypercalcaemia.
Gout.

4.4 Special warnings and precautions for use

Renal impairment/kidney transplantation
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
Medicinal products that affect the renin-angiotensin-aldosterone system, including angiotensin II receptor antagonists (AIIRAs), may increase blood urea and serum creatinine in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney.

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 AIIRAs 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 hyperaldosteronism generally will not respond to antihypertensive agents acting through inhibition of the renin-angiotensin-aldosterone system. Therefore the use of Atacand Plus is not recommended in this population.

Electrolyte imbalance
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).

Treatment with candesartan cilexetil may cause hyperkalaemia, especially in the presence of heart failure and/or renal impairment. Concomitant use of Atacand Plus and potassium-sparing diuretics, potassium supplements or salt substitutes or other medicinal products that may increase serum potassium levels (e.g. heparin sodium) may lead to increases in serum potassium. Monitoring of potassium should be undertaken as appropriate.
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. Dose adjustment of antidiabetic medicinal products, 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. At the doses contained in Atacand Plus, only minimal effects were observed. Thiazide diuretics increase serum uric acid concentration and may precipitate gout in susceptible patients.

Photosensitivity
Cases of photosensitivity reactions have been reported during use of thiazide diuretics (see section 4.8). If a photosensitivity reaction occurs, it is recommended to stop treatment. If re-administration of treatment is essential, it is recommended to protect areas exposed to the sun or to artificial UVA radiation.

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 medicinal products that affect this system including AIIRAs, 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.
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 erythaematosus has been reported with the use of thiazide diuretics.

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

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.

Pregnancy
AIIRAs should not be initiated during pregnancy. Unless continued AIIRA therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments

which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with AIIRAs should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

4.5 Interaction with other medicinal products and other forms of interaction

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

The potassium depleting effect of hydrochlorothiazide could be expected to be potentiated by other medicinal products associated with potassium loss and hypokalaemia (e.g. other kaliuretic diuretics, laxatives, amphotericin, carbenoxolone, penicillin G sodium, salicylic acid derivates, steroids, ACTH).

Concomitant use of Atacand Plus and potassium-sparing diuretics, potassium supplements or salt substitutes or other medicinal products that may increase serum potassium levels (e.g. heparin sodium) may lead to increases in serum potassium. Monitoring of potassium should be undertaken as appropriate (see section 4.4).

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 medicinal products, and with the following medicinal products that could induce torsades de pointes:

- Class Ia antiarrhythmics (e.g. quinidine, hydroquinidine, disopyramide)
- Class III antiarrhythmics (e.g. amiodarone, sotalol, dofetilide, ibutilide)
- Some antipsychotics (e.g. thioridazine, chlorpromazine, levomepromazine, trifluoperazine, cyamemazine, sulpiride, sultopride, amisulpride, tiapride, pimozide, haloperidol, droperiodol)
- Others (e.g. bepridil, cisapride, diphemanil, erythromycin iv, halofantrin, ketanserin, mizolastin, pentamidine, sparfloxacine, terfenadine, vincamine iv)

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with Angiotensin Converting Enzyme (ACE) inhibitors or hydrochlorothiazide. A similar effect has also been reported with AIIRAs. Use of candesartan and hydrochlorothiazide with lithium is not recommended. If the combination proves necessary, careful monitoring of serum lithium levels is recommended.

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

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 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 of nondepolarising 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 the dose 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 medicinal products (e.g. cyclophosphamide, methotrexate) and potentiate their myelosuppressive effects.

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

Treatment with a thiazide diuretic may impair glucose tolerance. Dose adjustment of antidiabetic medicinal products, including insulin, may be required. Metformin should be used with caution because of the risk of lactic acidosis induced by possible functional renal failure linked to hydrochlorothiazide.

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.

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

Concomitant treatment with baclofen, amifostin, tricyclic antidepressants or neuroleptics may lead to enhancement of the antihypertensive effect and may induce hypotension.

4.6 Pregnancy and lactation

Pregnancy

Angiotensin II Receptor Antagonists (AIIRAs):

The use of AIIRAs is not recommended during the first trimester of pregnancy (see section 4.4). The use of AIIRAs is contraindicated during the second and third trimesters of pregnancy (see sections 4.3 and 4.4).

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Whilst there is no controlled epidemiological data on the risk with AIIRAs, similar risks may exist for this class of drugs. Unless continued AIIRA therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with AIIRAs should be stopped immediately and, if appropriate, alternative therapy should be started.

Exposure to AIIRA therapy during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia) (see section 5.3).
Should exposure to AIIRAs have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.
Infants whose mothers have taken AIIRAs should be closely observed for hypotension (see sections 4.3 and 4.4).

Hydrochlorothiazide:
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 the second and third trimesters may compromise foeto-placental perfusion and may cause foetal and neonatal effects like icterus, disturbance of electrolyte balance and thrombocytopenia.
Hydrochlorothiazide should not be used for gestational oedema, gestational hypertension or preeclampsia due to the risk of decreased plasma volume and placental hypoperfusion, without a beneficial effect on the course of the disease.
Hydrochlorothiazide should not be used for essential hypertension in pregnant women except in rare situations where no other treatment could be used.

Lactation

Angiotensin II Receptor Antagonists (AIIRAs):
Because no information is available regarding the use of Atacand Plus during breastfeeding, Atacand Plus is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.

Hydrochlorothiazide:
Hydrochlorothiazide is excreted in human milk in small amounts. Thiazides in high doses causing intense diuresis can inhibit the milk production. The use of Atacand Plus during breast-feeding is not recommended.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. When driving vehicles or operating machines, it should be taken into account that occasionally dizziness or weariness may occur during treatment with Atacand Plus.

4.8 Undesirable effects

In controlled clinical studies with candesartan cilexetil/hydrochlorothiazide adverse reactions 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 clinical trials with candesartan cilexetil/hydrochlorothiazide, adverse reactions were limited to those that were reported previously with candesartan cilexetil and/or hydrochlorothiazide.

The table below presents adverse reactions with candesartan cilexetil from clinical trials and post marketing experience. In a pooled analysis of clinical trial data of hypertensive patients, adverse reactions with candesartan cilexetil were defined based on an incidence of adverse events with candesartan cilexetil at least 1% higher than the incidence seen with placebo.

The frequencies used in the tables throughout section 4.8 are: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000).

System Organ Class	Frequency	Undesirable Effect
Infections and infestations	Common	Respiratory infection
Blood and lymphatic system disorders	Very rare	Leukopenia, neutropenia and agranulocytosis
Metabolism and nutrition disorders	Very rare	Hyperkalaemia, hyponatraemia
Nervous system disorders	Common	Dizziness/vertigo, headache
Respiratory, thoracic and mediastinal disorders	Very rare	Cough
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 and connective tissue 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 table below presents adverse reactions with hydrochlorothiazide monotherapy usually with doses of 25 mg or higher.

System Organ Class	Frequency	Undesirable Effect
Blood and lymphatic system disorders	Rare	Leukopenia, neutropenia/agranulocytosis, thrombocytopenia, aplastic anaemia, bone marrow depression, haemolytic anaemia

System Organ Class	Frequency	Undesirable Effect
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 erythaematosus-like reactions, reactivation of cutaneous lupus erythaematosus
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

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 overdose with Atacand Plus. The following measures are, however, suggested in case of overdose.

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 medicinal products 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: 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 AIIRA, 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, AIIRAs 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 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 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 the combination losartan/hydrochlorothiazide 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 optimally 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/hydrochlorothiazide 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 substance 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.

Biotransformation 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 medicinal products 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. 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 metabolised 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 4.2).

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 two studies, both including patients with mild to moderate hepatic impairment, there was an increase in the mean AUC of candesartan of approximately 20% in one study and 80% in the other study (see section 4.2). There is no experience in patients with severe hepatic impairment.

Hydrochlorothiazide
The terminal $t_{½}$ 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).

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

[To be completed nationally]

6.2 Incompatibilities

[To be completed nationally]

6.3 Shelf life

[To be completed nationally]

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions.

6.5 Nature and contents of container

[To be completed nationally]

6.6 Special precautions for disposal and other handling

No special requirements

7. MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

[To be completed nationally]

Detailed information on this medicinal product is available on the website of {name of MS/Agency}

Labelling

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

CARTON FOR BLISTER / CARTON FOR BOTTLE / LABEL FOR BOTTLE

1. NAME OF THE MEDICINAL PRODUCT

Atacand Plus and associated names (see Annex I) 8 mg/12.5 mg tablets
Atacand Plus and associated names (see Annex I) 16 mg/12.5 mg tablets
Atacand Plus and associated names (see Annex I) 32 mg/12.5 mg tablets
Atacand Plus and associated names (see Annex I) 32 mg/25 mg tablets

[See Annex I - To be completed nationally]

candesartan cilexetil/hydrochlorothiazide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

[To be completed nationally]

3. LIST OF EXCIPIENTS

Contains lactose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

[To be completed nationally]

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

[To be completed nationally]

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

[To be completed nationally]

MINIMUM PARTICULARS TO APPEAR ON BLISTERS

Non-Perforated foil, Perforated Foil

1. NAME OF THE MEDICINAL PRODUCT

Atacand Plus and associated names (see Annex I) 8 mg/12.5 mg tablets
Atacand Plus and associated names (see Annex I) 16 mg/12.5 mg tablets
Atacand Plus and associated names (see Annex I) 32 mg/12.5 mg tablets
Atacand Plus and associated names (see Annex I) 32 mg/25 mg tablets

[See Annex I - To be completed nationally]

candesartan cilexetil/hydrochlorothiazide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

MINIMUM PARTICULARS TO APPEAR ON BLISTERS

Non-Perforated calendar foil (7, 14, 28, 56 and 98 tablets)

1. NAME OF THE MEDICINAL PRODUCT

Atacand Plus and associated names (see Annex I) 8 mg/12.5 mg tablets
Atacand Plus and associated names (see Annex I) 16 mg/12.5 mg tablets
Atacand Plus and associated names (see Annex I) 32 mg/12.5 mg tablets
Atacand Plus and associated names (see Annex I) 32 mg/25 mg tablets

[See Annex I - To be completed nationally]

candesartan cilexetil/hydrochlorothiazide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Mon Tue Wed Thur Fri Sat Sun

Package leaflet

PACKAGE LEAFLET: INFORMATION FOR THE USER

Atacand Plus and associated names (see Annex I) 8 mg/12.5 mg tablets
Atacand Plus and associated names (see Annex I) 16 mg/12.5 mg tablets
Atacand Plus and associated names (see Annex I) 32 mg/12.5 mg tablets
Atacand Plus and associated names (see Annex I) 32 mg/25 mg tablets

[See Annex I - To be completed nationally]
candesartan cilexetil/hydrochlorothiazide

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT ATACAND PLUS IS AND WHAT IT IS USED FOR

The name of your medicine is Atacand Plus. It is used for treating high blood pressure (hypertension) in adult patients. It contains two active ingredients: candesartan cilexetil and hydrochlorothiazide. These work together to lower your blood pressure.

- Candesartan cilexetil belongs to a group of medicines called angiotensin II receptor antagonists. It makes your blood vessels relax and widen. This helps to lower your blood pressure.
- Hydrochlorothiazide belongs to a group of medicines called diuretics (water tablets). It helps your body to get rid of water and salts like sodium in your urine. This helps to lower your blood pressure.

Your doctor may prescribe Atacand Plus if your blood pressure has not been properly controlled by candesartan cilexetil or hydrochlorothiazide alone.

2. BEFORE YOU TAKE ATACAND PLUS

Do not take Atacand Plus if:
- you are allergic (hypersensitive) to candesartan cilexetil or hydrochlorothiazide or any of the other ingredients of Atacand Plus (see section 6).
- you are allergic to sulphonamide medicines. If you are not sure if this applies to you, please ask your doctor.
- you are more than 3 months pregnant (it is also better to avoid Atacand Plus in early pregnancy – see pregnancy section).
- you have severe kidney problems.
- you have severe liver disease or biliary obstruction (a problem with the drainage of bile from the gall bladder).
- you have persistently low levels of potassium in your blood.
- you have persistently high levels of calcium in your blood.
- you have ever had gout.

If you are not sure if any of these apply to you, talk to your doctor or pharmacist before taking Atacand Plus.

Take special care with Atacand Plus
Before you take, or whilst you are taking Atacand Plus, tell your doctor if:
- you have diabetes.

- you have heart, liver or kidney problems.
- you have recently had a kidney transplant.
- you are vomiting, have recently had severe vomiting, or have diarrhoea.
- you have a disease of the adrenal gland called Conn's syndrome (also called primary hyperaldosteronism).
- you have ever had a disease called systemic lupus erythaematosus (SLE)
- you have low blood pressure
- you have ever had a stroke.
- you have ever had allergy or asthma.
- you must tell your doctor if you think you are (or might become) pregnant. Atacand Plus is not recommended in early pregnancy, and must not be taken if you are more than 3 months pregnant, as it may cause serious harm to your baby if used at that stage (see pregnancy section).

Your doctor may want to see you more often and do some tests if you have any of these conditions.

If you are going to have an operation, tell your doctor or dentist that you are taking Atacand Plus. This is because Atacand Plus, when combined with some anaesthetics, may cause a drop in blood pressure.

Atacand Plus may cause increased sensitivity of the skin to sun.

Use in children
There is no experience with the use of Atacand Plus in children (below the age of 18 years). Therefore Atacand Plus should not be given to children.

Using other medicines
Please tell your doctor or pharmacist if you are using or have recently used any other medicines, including medicines obtained without a prescription. Atacand Plus can affect the way some other medicines work and some medicines can have an effect on Atacand Plus. If you are using certain medicines, your doctor may need to do blood tests from time to time.

In particular, tell your doctor if you are using any of the following medicines:
- Other medicines to help lower your blood pressure, including beta-blockers, diazoxide and Angiotensin Converting Enzyme (ACE) inhibitors such as enalapril, captopril, lisinopril or ramipril.
- Non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, naproxen, diclofenac, celecoxib or etoricoxib (medicines to relieve pain and inflammation).
- Acetylsalicylic acid (if you are taking more than 3 g each day) (medicine to relieve pain and inflammation).
- Potassium supplements or salt substitutes containing potassium (medicines that increase the amount of potassium in your blood).
- Calcium or Vitamin D supplements.
- Medicines to lower your cholesterol, such as colestipol or cholestyramine.
- Medicines for diabetes (tablets or insulin).
- Medicines to control your heart beat (antiarrhythmic agents) such as digoxin and beta-blockers.
- Medicines that can be affected by potassium blood levels such as some antipsychotic medicines.
- Heparin (a medicine for thinning the blood)
- Water tablets (diuretics).
- Laxatives.
- Penicillin (an antibiotic).
- Amphotericin (for the treatment of fungal infections).
- Lithium (a medicine for mental health problems).
- Steroids such as prednisolone.
- Pituitary hormone (ACTH).
- Medicines to treat cancer.
- Amantadine (for the treatment of Parkinson's disease or for serious infections caused by viruses).
- Barbiturates (a type of sedative also used to treat epilepsy).
- Carbenoxolone (for treatment of oesophageal disease, or oral ulcers).
- Anticholinergic agents such as atropine and biperiden.
- Cyclosporine, a medicine used for organ transplant to avoid organ rejection.
- Other medicines that may lead to enhancement of the antihypertensive effect such as baclofen (a medicine for relief of spasticity), amifostin (used in cancer treatment) and some antipsychotic medicines.

Taking Atacand Plus with food and drink (in particular alcohol)

- You can take Atacand Plus with or without food.
- When you are prescribed Atacand Plus, discuss with your doctor before drinking alcohol. Alcohol may make you feel faint or dizzy.

Pregnancy and breast-feeding
Pregnancy
You must tell your doctor if you think you are (or might become) pregnant. Your doctor will normally advise you to stop taking Atacand Plus before you become pregnant or as soon as you know you are pregnant and will advise you to take another medicine instead of Atacand Plus. Atacand Plus is not recommended in early pregnancy, and must not be taken when more than 3 months pregnant, as it may cause serious harm to your baby if used after the third month of pregnancy.

Breast-feeding
Tell your doctor if you are breast-feeding or about to start breast-feeding. Atacand Plus is not recommended for mothers who are breast-feeding, and your doctor may choose another treatment for you if you wish to breast-feed, especially if your baby is newborn, or was born prematurely.

Driving and using machines
Some people may feel tired or dizzy when taking Atacand Plus. If this happens to you, do not drive or use any tools or machines.

Important information about some of the ingredients of Atacand Plus
Atacand Plus contains lactose which is a type of sugar. If you have been told by doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. HOW TO TAKE ATACAND PLUS

Always take Atacand Plus exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure. It is important to keep taking Atacand Plus every day.
The usual dose of Atacand Plus is one tablet once a day
Swallow the tablet with a drink of water.
Try to take the tablet at the same time each day. This will help you to remember to take it.

If you take more Atacand Plus than you should
If you take more Atacand Plus than prescribed by your doctor, contact a doctor or pharmacist immediately for advice.

If you forget to take use Atacand Plus
Do not take a double dose to make up for a forgotten tablet. Just take the next dose as normal.

If you stop taking Atacand Plus
If you stop taking Atacand Plus, your blood pressure may increase again. Therefore do not stop taking Atacand Plus without first talking to your doctor.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Atacand Plus can cause side effects, although not everybody gets them. It is important that you are aware of what these side effects may be. Some of the side effects of Atacand Plus are caused by candesartan cilexetil and some are caused by hydrochlorothiazide.

Stop taking Atacand Plus and seek medical help immediately if you have any of the following allergic reactions:
- difficulties in breathing, with or without swelling of the face, lips, tongue and/or throat.
- swelling of the face, lips, tongue and/or throat, which may cause difficulties in swallowing.
- severe itching of the skin (with raised lumps).

Atacand Plus may cause a reduction in number of white blood cells. Your resistance to infection may be decreased and you may notice tiredness, an infection or a fever. If this happens contact your doctor. Your doctor may occasionally do blood tests to check whether Atacand Plus has had any effect on your blood (agranulocytosis).

Other possible side effects include:

Common (affects 1 to 10 users in 100)

- Changes in blood test results**:**
  - A reduced amount of sodium in your blood. If this is severe then you may notice weakness, lack of energy, or muscle cramps.
  - An increased or reduced amount of potassium in your blood, especially if you already have kidney problems or heart failure. If this is severe, you may notice tiredness, weakness, irregular heartbear or pins and needles.
  - An increased amount of cholesterol, sugar or uric acid in your blood.
- Sugar in your urine.
- Feeling dizzy/spinning sensation or weak.
- Headache.
- Respiratory infection.

Uncommon (affects less than 1 user in 100)

- Low blood pressure. This may make you feel faint or dizzy.
- Loss of appetite, diarrhoea, constipation, stomach irritation.
- Skin rash, lumpy rash (hives), rash caused by sensitivity to sunlight.

Rare (affects less than 1 user in 1,000)

- Jaundice (yellowing of the skin or the whites of your eyes). If this happens to you, contact your doctor immediately.
- Effects on how your kidneys work, especially if you have kidney problems or heart failure.
- Difficulty in sleeping, depression, being restless.
- Tingling or prickling in your arms or legs.
- Blurred vision for a short time.
- Abnormal heart beat.
- Breathing difficulties (including lung inflammation and fluid in the lungs).
- High temperature (fever).
- Inflammation of the pancreas. This causes moderate to severe pain in the stomach.
- Muscle cramps.
- Damage to blood vessels causing red or purple dots in the skin.
- A reduction in your red or white blood cells or platelets. You may notice tiredness, an infection, fever or easy bruising.
- A severe rash, that develops quickly, with blistering or peeling of the skin and possibly blistering in the mouth.
- Worsening of existing lupus erythaematosus-like reactions or appearance of unusual skin reactions.

Very rare (affects less than 1 user in 10,000)

- Swelling of the face, lips, tongue and/or throat.
- Itching.
- Back pain, pain in joints and muscles.
- Changes in how your liver is working, including inflammation of the liver (hepatitis).You may notice tiredness, yellowing of your skin and the whites of your eyes and flu like symptoms.
- Cough
- Nausea.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE ATACAND PLUS

[To be completed nationally]

- Keep out of the reach and sight of children.
- This medicinal product does not require any special temperature storage conditions.
- Do not use Atacand Plus after the expiry date which is stated on the carton, blister pack or bottle. The expiry date refers to the last day of that month.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Atacand Plus contains

[To be completed nationally]

What Atacand Plus looks like and contents of the pack

[To be completed nationally]

Marketing Authorisation Holder and Manufacturer

[See Annex I - To be completed nationally]

{Name and address of the manufacturer}
{tel}
{fax}
{e-mail}

This medicinal product is authorised in the Member States of the EEA under the following names:

Name	**Member State**
Atacand Plus	Austria, Belgium, Cyprus, Czech Republic, Estonia, Germany, Greece, Finland, Hungary, Iceland, Ireland, Luxembourg, The Netherlands, Norway, Slovakia, Slovenia, Spain, Sweden
Hytacand	France, Portugal
Atacand Zid	Denmark
Ratacand Plus	Italy

This leaflet was last approved in {MM/YYYY}.

[To be completed nationally]