

PRODUCT MONOGRAPH

Pr ATACAND® PLUS

candesartan cilexetil/hydrochlorothiazide tablets

16 mg / 12.5 mg, 32 mg / 12.5 mg and 32 mg / 25 mg

Angiotensin II AT₁ Receptor Blocker + Diuretic

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Pr ATACAND® PLUS

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Nonmedicinal Ingredients
Oral	Tablet: 16 mg / 12.5 mg, 32 mg / 12.5 mg and 32 mg / 25 mg	Calcium carboxymethylcellulose, hydroxypropyl cellulose, iron oxide, lactose, magnesium stearate, maize starch, polyethylene glycol

INDICATIONS AND CLINICAL USE

ATACAND PLUS (candesartan cilexetil/hydrochlorothiazide) is indicated for the treatment of essential hypertension in patients for whom combination therapy is appropriate.

ATACAND PLUS is not indicated for initial therapy (see DOSAGE AND ADMINISTRATION).

The dosage of ATACAND PLUS must be individualized. The dose of ATACAND PLUS should be determined by titration of the individual components.

Geriatrics (> 65 years of age): No overall differences in safety or effectiveness were observed between the younger and elderly patients but greater sensitivity of some older patients cannot be ruled out and appropriate caution is recommended.

Pediatrics (< 18 years of age): The safety and efficacy of ATACAND PLUS have not been established in children.

CONTRAINDICATIONS

ATACAND PLUS (candesartan cilexetil/hydrochlorothiazide) is contraindicated in:

- Patients who are hypersensitive to any component of this product (see DOSAGE FORMS, COMPOSITION AND PACKAGING).

- Patients with anuria and patients who are hypersensitive to other sulfonamide-derived drugs, because of the hydrochlorothiazide component (see WARNINGS AND PRECAUTIONS, Immune and ADVERSE REACTIONS, Post-Market Adverse Drug Reactions).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

When used in pregnancy, angiotensin receptor (AT₁) blockers (ARBs) can cause injury or even death of the developing fetus. When pregnancy is detected, ATACAND PLUS should be discontinued as soon as possible (see WARNINGS AND PRECAUTIONS, Special Populations, Pregnant Women).

Cardiovascular

Hypotension

Occasionally, symptomatic hypotension has occurred after administration of candesartan cilexetil. It is more likely to occur in patients who are volume-depleted by diuretic therapy, dietary salt restriction, dialysis, diarrhea or vomiting, or undergoing surgery with anaesthesia. In these patients, because of the potential fall in blood pressure, therapy should be started under close medical supervision. Similar considerations apply to patients with ischemic heart or cerebrovascular disease, in whom an excessive fall in blood pressure could result in myocardial infarction or cerebrovascular accident.

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.

Valvular Stenosis

There is concern on theoretical grounds that patients with aortic stenosis might be at particular risk of decreased coronary perfusion when treated with vasodilators because they do not develop as much afterload reduction.

Endocrine and Metabolism

Metabolism

Patients receiving thiazides, including hydrochlorothiazide (HCTZ), should be carefully observed for clinical signs of fluid and electrolyte imbalance (hyponatremia, hypochloremic alkalosis and hypokalemia).

Periodic determinations of serum electrolytes, to detect possible electrolyte disturbance, should be performed at appropriate intervals. Warning signs or symptoms of fluid and

electrolyte imbalance include dryness of the mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pain or cramps, muscle fatigue, hypotension, oliguria, tachycardia and gastrointestinal disturbances such as nausea and vomiting.

Hypokalemia may develop, especially with brisk diuresis, when severe cirrhosis is present, or after prolonged therapy.

Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia can sensitize or exaggerate the response of the heart to the toxic effects of digitalis (e.g. increased ventricular irritability).

Any chloride deficit during thiazide therapy is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather. Appropriate therapy is water restriction rather than administration of salt, except in rare instances, when the hyponatremia is life threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur or acute gout may be precipitated in certain patients receiving thiazide therapy.

Thiazides may decrease serum PBI (protein bound iodine) levels without signs of thyroid disturbance.

Thiazides have been shown to increase excretion of magnesium; this may result in hypomagnesemia.

Thiazides may decrease urinary calcium excretion and may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Treatment with a thiazide diuretic may impair glucose tolerance. Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy. However, at the doses contained in ATACAND PLUS (candesartan cilexetil/hydrochlorothiazide), minimal effects were observed.

Hepatic/Biliary/Pancreatic

Hepatic Impairment

Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid or electrolyte balance may precipitate hepatic coma (see DOSAGE AND ADMINISTRATION, Hepatic Impairment).

No studies were carried out with candesartan cilexetil/hydrochlorothiazide fixed combination in patients with impaired hepatic function.

Immune

Hypersensitivity Reactions

Sensitivity reactions to hydrochlorothiazide may occur in patients with or without a history of allergy or bronchial asthma.

The possibility of exacerbation or activation of systemic lupus erythematosus has been reported in patients treated with hydrochlorothiazide.

Peri-Operative Considerations

Thiazides may increase the responsiveness to tubocurarine.

Renal

Renal Impairment

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function have been seen in susceptible individuals. In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, such as patients with bilateral renal artery stenosis, unilateral renal artery stenosis to a solitary kidney, or severe congestive heart failure, treatment with agents that inhibit this system has been associated with oliguria, progressive azotemia, and rarely, acute renal failure and/or death. In susceptible patients, concomitant diuretic use may further increase risk.

Use of candesartan cilexetil should include appropriate assessment of renal function. Thiazides should be used with caution.

Because of the hydrochlorothiazide component, ATACAND PLUS is not recommended in patients with severe renal impairment (creatinine clearance < 30 mL/min/1.73 m² BSA).

Azotemia

Azotemia may be precipitated or increased by hydrochlorothiazide. Cumulative effects of the drug may develop in patients with impaired renal function. If increasing azotemia and oliguria occur during treatment of severe progressive renal disease the diuretic should be discontinued.

Special Populations

Pregnant Women: drugs that act directly on the renin-angiotensin-aldosterone-system (RAAS) can cause fetal and neonatal morbidity and death when administered to pregnant women. When pregnancy is detected, ATACAND PLUS should be discontinued as soon as possible.

The use of ARBs is not recommended during pregnancy. Epidemiological evidence regarding the risk of teratogenicity following exposure to angiotensin converting enzyme inhibitors (another class of therapeutic products interfering with the RAAS) during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Given the current evidence available on the risk with ARBs, similar risks may exist for this class of drugs. Patients planning pregnancy should be changed to alternative anti-

hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with angiotensin receptor (AT₁) blockers should be stopped immediately, and, if appropriate, alternative therapy should be started.

The use of ARBs 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).

Infants with a history of in utero exposure to ARBs should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as a means of reversing hypotension and/or substituting for impaired renal function; however, limited experience with those procedures has not been associated with significant clinical benefit. Candesartan cilexetil is not removed from plasma by dialysis.

Thiazides cross the placental barrier and appear in cord blood. The routine use of diuretics in otherwise healthy pregnant women is not recommended and exposes mother and fetus to unnecessary hazard including fetal or neonatal jaundice, thrombocytopenia and possibly other adverse experiences which have occurred in the adult. Diuretics do not prevent development of toxemia of pregnancy and there is no satisfactory evidence that they are useful in the treatment of toxemia.

Animal Data: oral doses ≥ 10 mg candesartan cilexetil/kg/day administered to pregnant rats during late gestation and continued through lactation were associated with reduced survival and an increased incidence of hydronephrosis in the offspring. Candesartan cilexetil given to pregnant rabbits at an oral dose of 3 mg/kg/day caused maternal toxicity (decreased body weight and death) but, in surviving dams, had no adverse effects on fetal survival, fetal weight, or external, visceral, or skeletal development. No maternal toxicity or adverse effects on fetal development were observed when oral doses up to 1000 mg candesartan cilexetil/kg/day were administered to pregnant mice.

Nursing Women: it is not known whether candesartan is excreted in human milk, but significant levels have been found in the milk of lactating rats. Thiazides appear in human milk. Because many drugs are excreted in human milk, and because of their potential for affecting the nursing infant adversely, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatrics (< 18 years of age): the safety and efficacy of ATACAND PLUS have not been established in children.

Geriatrics (> 65 years of age): no overall differences in safety or effectiveness were observed between the younger and elderly patients but greater sensitivity of some older patients cannot be ruled out and appropriate caution is recommended.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

ATACAND PLUS (candesartan cilexetil/hydrochlorothiazide) has been evaluated for safety in over 2500 patients treated for hypertension, including more than 700 treated for six months or more, and 500 for about one year or more. In placebo controlled double blind studies to support ATACAND PLUS 16 mg / 12.5 mg, candesartan cilexetil/hydrochlorothiazide combination was administered to 1025 hypertensive patients. Approximately 600 patients received ATACAND PLUS 16 mg / 12.5 mg. The overall exposure amounts to 977 patient-years. Safety of the higher strength combinations of ATACAND PLUS, 32 mg / 12.5 mg and 32 mg / 25 mg, has also been evaluated. In controlled clinical studies 718 patients were treated with candesartan/hydrochlorothiazide 32 mg / 12.5 mg and 1155 patients were treated with 32 mg / 25 mg; the total exposure in patient years in these studies was 107.8 and 175.3 years, respectively.

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

In controlled clinical studies, discontinuation due to adverse events occurred in 2.3-3.3% and 2.7-4.3% of patients treated with ATACAND PLUS and placebo, respectively. In studies to support the 16 mg / 12.5 mg strength, the incidence of serious adverse events observed with candesartan cilexetil/hydrochlorothiazide was 2.7% (71 out of 2582 patients). The incidence of serious adverse events was lower in the candesartan cilexetil/hydrochlorothiazide 32 mg / 12.5 mg and 32 mg / 25 mg dosage groups with the highest frequency of 0.8% (5 out of 664 patients) observed in the 32 mg / 25 mg group.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

In the double blind placebo controlled studies to support candesartan cilexetil/hydrochlorothiazide 16 mg / 12.5 mg, the overall incidence of adverse events showed no association with age or gender. In these studies the following adverse events reported with candesartan cilexetil/hydrochlorothiazide occurred in $\geq 1\%$ of patients, regardless of drug relationship (see Table 1).

Table 1 Adverse events reported with candesartan cilexetil/hydrochlorothiazide in $\geq 1\%$ of patients regardless of causality in studies supporting the 16 mg / 12.5 mg strength

	Candesartan cilexetil/ hydrochloro- thiazide (n=1 025)	Candesartan cilexetil (n=749)	Hydrochloro- thiazide (n=603)	Placebo (n=526)
	%	%	%	%
Body as a Whole				
back pain	3.8	5.5	5.1	3.0
arthralgia	1.5	1.3	1.3	0.8
fatigue	1.4	1.2	1.7	1.0
abdominal pain	1.3	1.7	0.7	1.1
Urinary				
urinary tract infection	1.6	1.3	1.8	1.0
Digestive				
nausea	1.5	0.9	1.2	0.6
diarrhea	1.1	0.7	0.5	1.3
gastroenteritis	1.0	0.5	1.0	0.4
Cardiovascular				
tachycardia	1.3	0.9	1.2	0.8
ECG abnormal	1.2	1.2	0.3	0.8
edema peripheral	1.1	1.6	2.2	1.3
chest pain	1.0	0.7	1.0	0.6
Metabolic Disorders				
hyperuricemia	1.1	0.7	0.8	0.4
hyperglycemia	1.0	0.9	0.5	0.2
Nervous/Psychiatric				
headache	4.3	7.6	7.6	7.0
dizziness	3.1	3.9	2.0	1.5
inflicted injury	2.0	2.0	3.0	1.9
Respiratory				
upper respiratory tract infection	3.7	5.1	5.6	1.9
influenza-like symptoms	2.8	2.3	3.0	2.9

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	Candesartan cilexetil/hydrochlorothiazide (n=1 025)	Candesartan cilexetil (n=749)	Hydrochlorothiazide (n=603)	Placebo (n=526)
	%	%	%	%
sinusitis	2.3	2.9	3.5	1.9
bronchitis	2.1	2.8	2.5	2.5
pharyngitis	1.4	0.9	1.0	1.7
cough	0.9	2.3	1.7	1.0
rhinitis	1.2	1.5	1.2	0.4

In double blind, controlled studies with candesartan cilexetil/hydrochlorothiazide 32 mg / 12.5 mg, and 32 mg / 25 mg the following adverse events reported with candesartan cilexetil/hydrochlorothiazide occurred in $\geq 1\%$ of patients, regardless of drug relationship (see Table 2).

Table 2 Adverse events reported with candesartan cilexetil/hydrochlorothiazide 32 mg / 12.5 mg and 32 mg / 25 mg in $\geq 1\%$ of patients regardless of causality

	Candesartan cilexetil/hydrochlorothiazide (n=1 873)		Candesartan cilexetil (n=1188)	Hydrochlorothiazide (n=540)	Placebo (n=163)
	32 mg / 12.5 mg (n= 718)	32 mg / 25 mg (n= 1155)			
	%	%	%	%	%
Body as a Whole					
back pain	2.4	1.6	1.1	0.6	2.5
fatigue	1.1	0.9	0.8	0.4	2.5
arthralgia	0.6	1.1	0.6	1.1	1.8
Digestive					
diarrhea	1.1	0.4	0.7	0.4	1.8
Metabolic Disorders					
dyslipidaemia	3.3	2.5	1.9	0.4	0
Nervous/Psychiatric					

Table 2 Adverse events reported with candesartan cilexetil/hydrochlorothiazide 32 mg / 12.5 mg and 32 mg / 25 mg in \geq 1% of patients regardless of causality

	Candesartan cilexetil/ hydrochlorothiazide (n=1 873)		Candesartan cilexetil (n=1188)	Hydrochloro- thiazide (n=540)	Placebo (n=163)
	32 mg / 12.5 mg (n= 718)	32 mg / 25 mg (n= 1155)			
	%	%	%	%	%
dizziness	2.5	2.9	1.3	2.4	0.6
headache	2.4	2.0	5.1	7.6	7.4
Respiratory					
cough	1.4	0.7	0.6	1.3	1.2
nasopharyngitis	1.3	1.4	1.0	0.6	0
upper respiratory tract infection	1.3	0.3	1.7	3.5	5.5
bronchitis	1.1	0.9	1.0	1.3	1.2

Less Common Clinical Trial Adverse Drug Reactions (<1%)

Candesartan cilexetil

The following adverse events were reported at an incidence of <1% in controlled clinical trials (in more than one patient, with higher frequency than placebo):

Body as a Whole: allergy, asthenia, pain, syncope.

Cardiovascular: angina pectoris, circulatory failure, flushing, hypotension, myocardial infarction, peripheral ischemia, thrombophlebitis.

Central and Peripheral Nervous System: hypertonia, hypoesthesia, paresthesia, vertigo.

Gastrointestinal: constipation, dyspepsia, dry mouth, toothache.

Hearing: tinnitus.

Metabolic and Nutritional: diabetes mellitus, hyperkalaemia, hyponatraemia.

Musculoskeletal: arthritis, arthropathy, myalgia, myopathy, skeletal pain, tendon disorder.

Blood: anemia, epistaxis.

Psychiatric: depression, impotence, neurosis.

Reproductive: menopausal symptoms.

Resistance Mechanism: otitis.

Respiratory: laryngitis.

Skin: eczema, pruritus, rash, skin disorder, sweating, (rarely) urticaria.

Urinary: abnormal urine, cystitis.

Vision: conjunctivitis.

There was no clear indication of dose-response relationship for any of the most common adverse events.

Abnormal Hematologic and Clinical Chemistry Findings

Laboratory Test Findings

In controlled clinical trials, clinically important changes in standard laboratory parameters were rarely associated with administration of ATACAND PLUS.

Liver Function Tests: in controlled clinical trials, elevations of ALT (> 3 times the upper limit of normal) occurred in 0.9% of patients treated with ATACAND PLUS compared to 0% of patients receiving placebo. Minor increases in serum AST have been observed in single patients receiving candesartan cilexetil/hydrochlorothiazide.

Serum Potassium, Sodium: a small decrease (mean decrease of 0.1 mmol/L) in serum potassium was observed in patients treated with ATACAND PLUS but was rarely of clinical importance. Values of serum potassium below the predefined lower critical limit were recorded in 0.6% of patients in controlled clinical trials with ATACAND PLUS. An increase in serum potassium has rarely been observed with ATACAND PLUS. A decrease in sodium has been observed with ATACAND PLUS.

Hemoglobin and Hematocrit: small decreases in hemoglobin were observed in patients treated with ATACAND PLUS but were rarely of clinical importance. Values of hemoglobin below the predefined critical limit were recorded in 0.9% of patients in controlled clinical trials with ATACAND PLUS.

Blood glucose: in controlled clinical trials, elevations of blood glucose occurred in 1.0% of patients treated with ATACAND PLUS compared to 0.2% of patients receiving placebo.

Hyperuricemia: increases in serum uric acid were found in 1.1% of patients treated with ATACAND PLUS and 0.4% of patients treated with placebo.

Creatinine, Urea: An increase in creatinine and urea has been observed with ATACAND PLUS.

Post-Market Adverse Drug Reactions

Candesartan cilexetil

Angioedema, (involving swelling of the face, lips and/or tongue) has been reported rarely in patients treated with candesartan cilexetil.

In other post-marketing experience, renal impairment, including renal failure in susceptible patients, has been observed (see WARNINGS AND PRECAUTIONS, Renal, – Renal Impairment for definition of susceptible patients).

Very rare cases of abnormal hepatic function or hepatitis have also been reported.

Other adverse events reported for candesartan cilexetil where a causal relationship could not be established include very rare cases of leukopenia, neutropenia and agranulocytosis.

Cases of muscle pain, muscle weakness, myositis and rhabdomyolysis have been reported in patients receiving angiotensin II receptor blockers.

Hydrochlorothiazide

Potentially serious clinical adverse events have been reported to occur with hydrochlorothiazide, such as: jaundice (intrahepatic cholestatic jaundice), pancreatitis, leukopenia, neutropenia/agranulocytosis, thrombocytopenia, aplastic anemia, haemolytic anemia, photosensitivity reactions, necrotising angitis (vasculitis), toxic epidermal necrolysis, anaphylactic reactions, respiratory distress (including pneumonitis and pulmonary edema), hypokalemia, renal dysfunction and interstitial nephritis.

DRUG INTERACTIONS

Overview

Warfarin

When candesartan cilexetil was administered at 16 mg once daily under steady state conditions, no pharmacodynamic effect on prothrombin time was demonstrated in subjects stabilized on warfarin.

Digoxin

Combination treatment with candesartan cilexetil and digoxin in healthy volunteers had no effect on AUC or C_{max} values for digoxin compared to digoxin alone. Similarly, combination treatment had no effect on AUC or C_{max} values for candesartan compared to candesartan cilexetil alone.

Thiazide-induced electrolyte disturbances may predispose to digitalis-induced arrhythmias.

d-Tubocurarine

Thiazide drugs may increase the responsiveness to tubocurarine.

Insulin

Insulin requirements in diabetic patients treated with diuretics may be increased, decreased or unchanged. Diabetes mellitus which has been latent may become manifest during thiazide administration.

Alcohol, Barbiturates or Narcotics

Thiazide diuretic potentiation of orthostatic hypotension may occur.

Corticosteroids, ACTH

Intensified electrolyte depletion, particularly hypokalemia, may occur when given concomitantly with thiazide diuretics.

Pressor Amines (e.g., norepinephrine)

In the presence of thiazide diuretics possible decreased response to pressor amines may be seen but not sufficient to preclude their use.

Other

No significant drug interactions have been reported with glyburide, nifedipine or oral contraceptives co-administered with candesartan cilexetil to healthy volunteers.

Co-administration of thiazide diuretics may increase the incidence of hypersensitivity reactions to allopurinol, may increase the risk of adverse effects caused by amantadine, may enhance the hyperglycemic effect of diazoxide, and may reduce the renal excretion of cytotoxic drugs (e.g. cyclophosphamide, methotrexate) and potentiate their myelosuppressive effects.

The bioavailability of thiazide diuretics may be increased by anticholinergic agents (e.g. atropine, biperiden), apparently due to a decrease in gastrointestinal motility and the stomach emptying rate.

There have been reports in the literature of hemolytic anemia occurring with concomitant use of hydrochlorothiazide and methyl dopa.

Absorption of thiazide diuretics is decreased by cholestyramine.

Administration of thiazide diuretics with vitamin D or with calcium salts may potentiate the rise in serum calcium.

Concomitant treatment with cyclosporin may increase the risk of hyperuricemia and gout type complications.

Drug-Drug Interactions

The drugs listed in Table 3 are based on either drug interaction case reports or studies or potential interactions due to the expected magnitude and seriousness of the interaction (i.e. those identified as contraindicated).

Table 3 **Established or Potential Drug-Drug Interactions**

Candesartan cilexetil	Effect	Clinical Comment
Diuretics	Patients on diuretics, and especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with candesartan cilexetil.	The possibility of symptomatic hypotension with the use of ATACAND (candesartan cilexetil) can be minimized by discontinuing the diuretic prior to initiation of treatment and/or lowering the initial dose of candesartan cilexetil (see WARNINGS AND PRECAUTIONS, Cardiovascular, Hypotension and DOSAGE AND ADMINISTRATION). No drug interaction of clinical significance has been identified with thiazide diuretics.
Agents Increasing Serum Potassium	ATACAND decreases the production of aldosterone.	Potassium-sparing diuretics or potassium supplements should be given only for documented hypokalemia and with frequent monitoring of serum potassium. Potassium-containing salt substitutes should also be used with caution. Concomitant thiazide diuretic use may attenuate any effect that candesartan cilexetil may have on serum potassium.
Lithium Salts	As with other drugs which eliminate sodium, lithium clearance may be reduced. Lithium generally should not be given with diuretics. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity.	Serum lithium levels should be monitored carefully if lithium salts are to be administered.
NSAIDS	In some patients, the administration of a nonsteroidal anti-inflammatory agent/drug (NSAID) can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing and thiazide diuretics.	When ATACAND PLUS (candesartan cilexetil/hydrochlorothiazide) and NSAIDs are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained.

Drug-Food Interactions

ATACAND PLUS may be taken with or without food (see DOSAGE AND ADMINISTRATION).

DOSAGE AND ADMINISTRATION

Dosing Considerations

The dosage of ATACAND PLUS (candesartan cilexetil/hydrochlorothiazide) must be individualized. The fixed combination is not for initial therapy. The dose of ATACAND PLUS should be determined by titration of the individual components.

Recommended Dose and Dosage Adjustment

Once the patient has been stabilized on the individual components one ATACAND PLUS 16 mg / 12.5 mg, 32 mg / 12.5 mg or 32 mg / 25 mg tablet once daily may be taken if the doses on which the patient was stabilized are the same as those in the fixed combination (see INDICATIONS AND CLINICAL USE).

Initiation of therapy requires consideration of recent antihypertensive treatment, the extent of blood pressure elevation, salt restriction, and other pertinent clinical factors.

ATACAND PLUS should be taken once daily, at approximately the same time each day, with or without food.

Candesartan cilexetil Monotherapy

The recommended initial dose of candesartan cilexetil is 16 mg, once daily. Total daily doses of candesartan cilexetil should range from 8 to 32 mg. Doses higher than 32 mg do not appear to have a greater effect on blood pressure reduction, and there is relatively little experience with such doses. Most of the antihypertensive effect is present within 2 weeks and the maximal blood pressure reduction is generally obtained within 4 weeks. For patients with possible depletion of intravascular volume (e.g. patients treated with diuretics, particularly those with impaired renal function) consideration should be given to administration of a lower dose. If blood pressure is not controlled by ATACAND alone, a thiazide diuretic may be added (see DRUG INTERACTIONS, Drug-Drug Interactions, Diuretics).

Concomitant Diuretic Therapy

In patients receiving diuretics, candesartan cilexetil therapy should be initiated with caution, since these patients may be volume-depleted and thus more likely to experience hypotension following initiation of additional antihypertensive therapy.

Whenever possible, all diuretics should be discontinued two to three days prior to the administration of candesartan cilexetil, to reduce the likelihood of hypotension (see WARNINGS AND PRECAUTIONS, Cardiovascular, Hypotension). If this is not possible because of the patient's condition, candesartan cilexetil should be administered with caution

and the blood pressure monitored closely. Thereafter, the dosage should be adjusted according to the individual response of the patient.

Dosing Considerations in Special Populations

Hepatic Impairment

No dosage adjustment of ATACAND PLUS is necessary in patients with mild to moderate chronic liver disease.

Since dosage adjustment of candesartan cilexetil is necessary in patients with severely impaired hepatic function and/or cholestasis, and thiazide diuretics may precipitate hepatic coma, use of ATACAND PLUS is not recommended in these patients (see WARNINGS AND PRECAUTIONS, Hepatic Impairment).

Renal Impairment

No dosage adjustment of candesartan cilexetil is necessary in patients with mildly impaired renal function.

In patients with moderately or severely impaired renal function, or in patients undergoing dialysis, a lower initial dose of 4 mg should be considered.

The usual regimens of therapy with ATACAND PLUS may be followed as long as the patient's creatinine clearance is $> 30 \text{ mL/min/1.73 m}^2 \text{ BSA}$. In patients with more severe renal impairment, loop diuretics are preferred to thiazides, so ATACAND PLUS is not recommended.

Geriatrics (> 65 years of age)

No dose adjustment of ATACAND PLUS is necessary for elderly patients. As greater sensitivity of some older patients cannot be ruled out, appropriate caution is recommended (see WARNINGS AND PRECAUTIONS, Geriatrics).

Pediatrics (< 18 years of age)

The safety and efficacy of ATACAND PLUS have not been established in children.

Missed Dose

If a patient misses a dose of ATACAND PLUS and remembers within 12 hours, the patient should take the dose as soon as possible and then go back to the regular schedule. If it is more than 12 hours after the patient remembers, they should not take the missed dose; the next dose should be taken on time.

A double dose of ATACAND PLUS should never be taken to make up for a missed dose.

OVERDOSAGE

For management of suspected drug overdose, contact your regional Poison Control Centre.

No specific information is available on the treatment of overdose with ATACAND PLUS (candesartan cilexetil/hydrochlorothiazide). Treatment is symptomatic and supportive.

Candesartan cilexetil

Limited data are available in regard to overdose of candesartan cilexetil in humans. The most likely manifestations of overdose would be hypotension, dizziness and tachycardia; bradycardia could occur from reflex parasympathetic (vagal) stimulation. If symptomatic hypotension should occur, supportive 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, for example, isotonic saline solution. Sympathomimetic drugs may also be administered if the above-mentioned measures are not sufficient. In case reports detailing overdose (up to 672 mg candesartan cilexetil) patient recovery was uneventful.

Candesartan cilexetil is not removed from the plasma by hemodialysis.

Hydrochlorothiazide

The most common symptoms observed from overdose of hydrochlorothiazide are those caused by electrolyte depletion (hypokalemia, hyponatremia) and dehydration resulting from excessive diuresis. If digitalis has also been administered, hypokalemia may accentuate cardiac arrhythmias. The degree to which hydrochlorothiazide is removed by hemodialysis has not been established.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

ATACAND PLUS (candesartan cilexetil/hydrochlorothiazide) combines the actions of candesartan cilexetil, an angiotensin II AT₁ receptor blocker, and that of a thiazide diuretic, hydrochlorothiazide.

Candesartan cilexetil

Candesartan cilexetil antagonizes the action of angiotensin II by blocking the angiotensin type one (AT₁) receptor. Angiotensin II is the primary vasoactive hormone of the renin-angiotensin-aldosterone system with effects that include vasoconstriction, stimulation of aldosterone secretion, and renal reabsorption of sodium.

Candesartan cilexetil, a prodrug, is rapidly converted to the active drug, candesartan, during absorption from the gastrointestinal tract.

Candesartan blocks the vasoconstrictor and aldosterone secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT₁ receptor in many tissues, such as

vascular smooth muscle and the adrenal gland. Its action is therefore independent of the pathways for angiotensin II synthesis. There are also AT₂ receptors found in many tissues, but they play no known role in cardiovascular homeostasis to date. Candesartan has a much greater affinity (> 10,000-fold) for the AT₁ receptor than for the AT₂ receptor. The strong bond between candesartan and the AT₁ receptor is a result of tight binding to and slow dissociation from the receptor.

Candesartan does not inhibit angiotensin converting enzyme (ACE), also known as kininase II, the enzyme that converts angiotensin I to angiotensin II and degrades bradykinin, nor does it bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

Hydrochlorothiazide

Hydrochlorothiazide is a diuretic and antihypertensive which interferes with the renal tubular mechanism of electrolyte reabsorption. It 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. While this compound is predominantly a saluretic agent, *in vitro* studies have shown that it has a carbonic anhydrase inhibitory action which seems to be relatively specific for the renal tubular mechanism. It does not appear to be concentrated in erythrocytes or the brain in sufficient amounts to influence the activity of carbonic anhydrase in those tissues.

Hydrochlorothiazide is useful in the treatment of hypertension. It may be used alone or as an adjunct to other antihypertensive drugs. Hydrochlorothiazide does not affect normal blood pressure.

Pharmacodynamics

Candesartan cilexetil

Candesartan inhibits the pressor effects of angiotensin II infusion in a dose-dependent manner. After 1 week of once-daily dosing of 8 mg candesartan cilexetil, the pressor effect was inhibited by approximately 90% at peak (4-8 hours after dosing) with approximately 50% inhibition persisting at 24 hours. Plasma concentrations of angiotensin I, angiotensin II, and plasma renin activity, increased in a dose-dependent manner after single and repeated administration of candesartan cilexetil to healthy subjects and hypertensive patients. A decrease in the plasma concentration of aldosterone was observed when 32 mg of candesartan cilexetil was administered to hypertensive patients.

Hydrochlorothiazide

Onset of the diuretic action following oral administration occurs in 2 hours and the peak action in about 4 hours. Diuretic activity lasts about 6 to 12 hours.

Pharmacokinetics

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

Candesartan cilexetil

Absorption: following oral administration of candesartan cilexetil as a tablet, the absolute bioavailability of candesartan was estimated to be approximately 15%. After tablet ingestion, the peak serum concentration (C_{max}) is reached after 3-4 hours. Food does not affect the bioavailability of candesartan after candesartan cilexetil administration.

Distribution: the volume of distribution of candesartan is 0.13 L/kg. Candesartan is highly bound to plasma proteins (>99%) and does not penetrate red blood cells. The protein binding is constant at candesartan plasma concentrations well above the range achieved with recommended doses. In rats, it has been demonstrated that candesartan does cross the blood-brain barrier. It has also been demonstrated in rats that candesartan passes across the placental barrier and is distributed in the fetus.

Metabolism: candesartan cilexetil is rapidly and completely bioactivated by ester hydrolysis during absorption from the gastrointestinal tract to candesartan. It undergoes minor hepatic metabolism by O-deethylation to an inactive metabolite. *In vitro* studies indicate that cytochrome P450 isoenzyme CYP 2C9 is involved in the biotransformation of candesartan to its inactive metabolite. 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.

Excretion: total plasma clearance of candesartan is 0.37 mL/min/kg, with a renal clearance of 0.19 mL/min/kg. Candesartan is mainly excreted unchanged in urine and feces (via bile). When candesartan cilexetil is administered orally, about 26% of the dose is excreted as candesartan in urine. Following an oral dose of ^{14}C -labeled candesartan cilexetil, approximately 33% of radioactivity is recovered in urine and approximately 67% in feces. Following an intravenous dose of ^{14}C -labeled candesartan, approximately 59% of radioactivity is recovered in urine and approximately 36% in feces. Biliary excretion contributes to the elimination of candesartan. The elimination half-life of candesartan is approximately 9 hours. After single and repeated administration, the pharmacokinetics of candesartan are linear, for oral doses up to 32 mg. Candesartan and its inactive metabolite do not accumulate in serum upon repeated once-daily dosing.

Hydrochlorothiazide

Absorption: hydrochlorothiazide is rapidly absorbed from the gastrointestinal tract with an absolute bioavailability of approximately 70%. Concomitant food intake increases the absorption by approximately 15%.

Distribution: the bioavailability may decrease in patients with cardiac failure and pronounced edema. The plasma protein binding of hydrochlorothiazide is approximately 60%. The apparent volume of distribution is approximately 0.8 L/kg.

Excretion: 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 (8 hours) after administration of hydrochlorothiazide in combination with candesartan cilexetil. No accumulation of hydrochlorothiazide occurs after repeated doses of the combination compared to monotherapy.

The terminal $t_{1/2}$ of hydrochlorothiazide is prolonged in the elderly and in patients with renal failure or chronic heart failure.

Hydrochlorothiazide crosses the placental but not the blood-brain barrier and is excreted in breast milk.

Special Populations and Conditions

Geriatrics: the plasma concentration of candesartan was higher in the elderly (≥ 65 years) (C_{max} was approximately 50% higher, and AUC was approximately 80% higher) compared to younger subjects administered the same dose. The pharmacokinetics of candesartan were linear in the elderly, and candesartan and its inactive metabolite did not accumulate in the serum of these subjects upon repeated, once-daily administration.

Gender: no gender-related differences in the pharmacokinetics of candesartan have been observed.

Hepatic Insufficiency: in patients with mild to moderate hepatic impairment, there was an increase in the AUC of candesartan of approximately 20%. There was no drug accumulation in plasma in these patients. In patients with moderate to severe hepatic impairment, the C_{max} and AUC increased up to five times in a very small group administered a single dose of 16 mg candesartan (see DOSAGE AND ADMINISTRATION, Hepatic Impairment).

Renal Insufficiency: in patients with mild to moderate renal impairment (Cl_{creat} 31-60 mL/min/1.73m²), C_{max} and AUC of candesartan increased by 40-60% and 50-90%, respectively, but $t_{1/2}$ was not altered, compared to patients with normal renal function ($Cl_{creat} > 60$ mL/min/1.73m²) during repeated dosing. There was no drug accumulation in plasma in patients with mild to moderate renal impairment. The increases in C_{max} and AUC in patients with severe renal impairment (Cl_{creat} 15-30 mL/min/1.73m²) were 40-60% and 110%, respectively. The terminal $t_{1/2}$ of candesartan was approximately doubled in patients with severe renal impairment, and these changes resulted in some accumulation in plasma. The pharmacokinetics of candesartan in patients undergoing hemodialysis were similar to those in patients with severe renal impairment (see DOSAGE AND ADMINISTRATION, Renal Impairment).

STORAGE AND STABILITY

Store at 15-30°C.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Forms

ATACAND PLUS (candesartan cilexetil/hydrochlorothiazide) is available in tablets of 16 mg / 12.5 mg, 32 mg / 12.5 mg and 32 mg / 25 mg.

Composition

Each tablet contains candesartan cilexetil/hydrochlorothiazide 16 mg / 12.5 mg, 32 mg / 12.5 mg or 32 mg / 25 mg. Each tablet also contains the following non-medicinal ingredients: calcium carboxymethylcellulose, hydroxypropyl cellulose, iron oxide, lactose, magnesium stearate, maize starch and polyethylene glycol.

Packaging

ATACAND PLUS 16 mg / 12.5 mg tablets are peach, biconvex, oval tablets with a score and marked $\frac{\Delta}{CS}$ on one side, available in blister packs of 30 tablets.

ATACAND PLUS 32 mg / 12.5 mg tablets are yellow, biconvex, oval tablets with a score and marked $\frac{\Delta}{CJ}$ on one side, available in blister packs of 30 tablets.

ATACAND PLUS 32 mg / 25 mg tablets are pink, biconvex, oval tablets with a score and marked $\frac{\Delta}{CD}$ on one side, available in blister packs of 30 tablets.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Common Name:

candesartan cilexetil

+

Proper Name:

hydrochlorothiazide

Chemical Name:

(±)-1-(Cyclohexyloxycarbonyloxy)ethyl-2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1H-benzimidazole-7-carboxylate

+

6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulphonamide

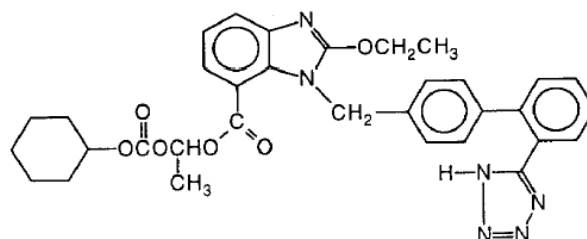
1,1-dioxide

Molecular Formula and Molecular Mass:

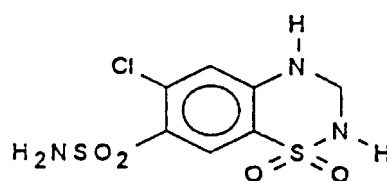
$C_{33}H_{34}N_6O_6 + C_7H_8ClN_3O_4S_2$

610.67 + 297.7

Structural Formula:



+



Physicochemical Properties:

Description:

Candesartan cilexetil is a white to off-white powder. The solubility in benzyl alcohol is 205 g/L, and the solubility in water is $< 5 \times 10^{-5}$ g/L.

Hydrochlorothiazide is a white, or almost white, odourless, crystalline powder.

Hydrochlorothiazide is very slightly soluble in water, soluble in acetone, and sparingly soluble in

ethanol (96%).

Melting Point:

Candesartan cilexetil: 163°C with decomposition.

Hydrochlorothiazide: 268°C

Partition Coefficient: Candesartan cilexetil

pH of Aqueous Layer	Partition Coefficient (K at 20°C)	
	Ethyl Ether	1-Octanol
1.1	> 1000	> 1000
6.9	> 1000	> 1000
8.9	141	> 1000

$$K = \frac{\text{Concentration of Candesartan Cilexetil in the organic layer}}{\text{Concentration of Candesartan Cilexetil in the aqueous layer}}$$

Partition Coefficient: Hydrochlorothiazide

pH of Aqueous Layer	Ionization constant (pKa at 25°C)
	n-Octanol
1.06	1.94
3.00	0.866
7.40	0.855

CLINICAL TRIALS

Candesartan cilexetil

In hypertension, candesartan cilexetil causes a dose-dependent reduction in arterial blood pressure. Systemic peripheral resistance is decreased, while heart rate, stroke volume and cardiac output are not significantly affected. No first-dose hypotension was observed during controlled clinical trials with candesartan cilexetil.

Most of the antihypertensive effect was seen within 2 weeks of initial dosing, and the full effect in 4 weeks. With once-daily dosing, blood pressure effect was maintained over 24 hours, with trough to peak ratios of blood pressure effect generally greater than 80%. Candesartan cilexetil had an additional blood pressure lowering effect when added to hydrochlorothiazide.

The antihypertensive effect was similar in men and women and in patients older and younger than 65. Candesartan was effective in reducing blood pressure regardless of race, although the effect was somewhat less in black patients (usually a low-renin population) than in Caucasian patients.

In long-term studies of up to 1 year, the antihypertensive effectiveness of candesartan cilexetil was maintained, and there was no rebound after abrupt withdrawal.

ATACAND also reduces urinary albumin excretion in patients with type II diabetes mellitus, hypertension, and microalbuminuria. In a 12-week study of 161 mildly hypertensive patients with type II diabetes mellitus, candesartan cilexetil 8 to 16 mg had no effect on mean HbA1c.

Comparative Effects

The antihypertensive efficacy of candesartan cilexetil and losartan potassium have been compared at their approved once daily maximum doses, 32 mg and 100 mg, respectively, in patients with mild to moderate essential hypertension. Candesartan cilexetil lowered systolic and diastolic blood pressure by 2 to 3 mm Hg on average more than losartan potassium when measured at the time of either peak or trough effect. Both agents were well tolerated.

Candesartan cilexetil/hydrochlorothiazide

Candesartan cilexetil and hydrochlorothiazide have additive antihypertensive effects. After administration of a single dose of ATACAND PLUS (candesartan cilexetil/hydrochlorothiazide) in hypertensive patients, 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 given once daily provides effective and smooth dose-dependent blood pressure reduction over 24 hours, with little difference between maximum and trough effects during the dosing interval and without reflex increase in heart rate. There is no indication of serious or exaggerated first dose hypotension or rebound effect after cessation of treatment.

Randomized placebo controlled studies with the combination of candesartan cilexetil and hydrochlorothiazide 32 mg / 12.5 mg or 32 mg / 25 mg once daily demonstrated a dose-dependent blood pressure lowering effect of ATACAND PLUS. The combination produced a statistically significant effect larger than candesartan cilexetil or hydrochlorothiazide monotherapy. The proportion of patients with controlled blood pressure was larger and the effect of the combination was dose-related.

Candesartan cilexetil/hydrochlorothiazide is similarly effective in patients irrespective of age and gender.

Pivotal Comparative Bioavailability Study

A randomized, single dose, double-blind, four-way crossover comparative bioavailability, study with a two-stage group sequential design under fasting conditions was conducted. In order to protect the overall α level at 0.05, the confidence intervals at the first and second stages of the study were set at 95% and 92%, respectively. Following an analysis at the first-stage, the rate and extent of absorption of candesartan and hydrochlorothiazide were measured and compared following a single oral dose of 1 x candesartan cilexetil/hydrochlorothiazide 32 mg / 25 mg tablet, 2 x candesartan cilexetil/hydrochlorothiazide 16 mg / 12.5 mg tablets, 1 x candesartan cilexetil 32 mg tablet and 2 x hydrochlorothiazide 12.5 mg tablets to 49 healthy male and female subjects. The results of the first-stage analysis for the comparison between 1 x candesartan cilexetil/hydrochlorothiazide 32 mg / 25 mg tablet and 2 x candesartan cilexetil/hydrochlorothiazide 16 mg / 12.5 mg tablets are provided below.

Table 4 Summary of the comparative bioavailability data for candesartan cilexetil

Candesartan (32 mg dose as either 1 x 32 mg / 25 mg or 2 x 16 mg / 12.5 mg) From measured data				
Geometric Mean Arithmetic Mean (CV%)				
Parameter	Test* (1 x 32 mg / 25 mg)	Reference† (2 x 16 mg / 12.5 mg)	% Ratio of Geometric Means ⁺⁺	95% Confidence Interval ⁺⁺
AUC _{0-t} (h*ng/mL)	3227.67 3349.34 (28.3)	2995.56 3128.75 (29.8)	107.87	101.71 - 114.39
AUC _{0-∞} (h*ng/mL)	3574.93 3702.46 (27.0)	3326.81 3456.97 (27.8)	107.71	101.40 - 114.42
C _{max} (ng/mL)	260.44 278.51 (38.6)	244.76 267.10 (42.0)	106.15	96.85 - 116.34
T _{max} (h) ⁺	4.50 (32.4)	4.35 (41.1)		

T _½ (h) ⁺	10.72 (40.7)	11.11 (37.3)		
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* ATACAND PLUS (candesartan cilexetil/hydrochlorothiazide) 32 mg / 25 mg tablets.

† ATACAND PLUS (candesartan cilexetil/hydrochlorothiazide) 16 mg / 12.5 mg tablets.

⁺ Expressed as arithmetic mean (CV%) only.

⁺⁺ Based on least square means estimates.

Table 5 Summary of the comparative bioavailability data for hydrochlorothiazide

Hydrochlorothiazide (25 mg dose as either 1 x 32 mg / 25 mg or 2 x 16 mg / 12.5 mg) From measured data				
Geometric Mean Arithmetic Mean (CV%)				
Parameter	Test* (1 x 32 mg / 25 mg)	Reference† (2 x 16 mg / 12.5 mg)	% Ratio of Geometric Means ⁺⁺	95% Confidence Interval ⁺⁺
AUC _{0-t} (h*ng/mL)	1386.75 1426.03 (24.6)	1361.19 1406.52 (26.5)	102.00	98.49 - 105.64
AUC _{0-∞} (h*ng/mL)	1441.79 1483.38 (24.8)	1415.59 1463.53 (26.7)	101.97	98.54 - 105.52
C _{max} (ng/mL)	218.27 224.92 (24.5)	206.16 212.83 (25.1)	106.06	99.23 - 113.37
T _{max} (h) ⁺	1.93 (43.5)	2.06 (48.0)		
T _½ (h) ⁺	8.57 (16.0)	8.56 (16.6)		

* ATACAND PLUS (candesartan cilexetil/hydrochlorothiazide) 32 mg / 25 mg tablets.

† ATACAND PLUS (candesartan cilexetil/hydrochlorothiazide) 16 mg / 12.5 mg tablets.

⁺ Expressed as arithmetic mean (CV%) only.

⁺⁺ Based on least square means estimates.

DETAILED PHARMACOLOGY

Animal Pharmacology

In an *in vitro* assay system, hydrochlorothiazide at 10⁻⁵ M did not affect the inhibition of binding of [¹²⁵I]AII to the AII receptor by candesartan.

HCTZ at 10 mg/kg/day had no effect on blood pressure in conscious spontaneously hypertensive rats. HCTZ combined with 0.1 or 1 mg/kg of candesartan cilexetil, synergistically intensified the reduction in blood pressure induced by candesartan cilexetil.

TOXICOLOGY

Acute Toxicity

Table 6 Acute Toxicity

Route	Species	Sex	LD ₅₀ (mg/kg) values
oral gavage	rat	Male Female	>2000 candesartan cilexetil & >1000 HCTZ

Chronic Toxicity

The toxic potential of candesartan cilexetil was evaluated in a series of repeated dose oral toxicity studies of up to 13 weeks in rats and dogs. The no toxic effect dose level for candesartan cilexetil/hydrochlorothiazide was 1/10 mg/kg/day in rats.

Table 7 Toxicity Upon Repeated Oral Administration

Species/ Strain	No. Of Animals per Group	Duration and Route of Adminis- tration	Daily Dose candesartan cilexetil/HCTZ (mg/kg)	Results
Rat / Fischer 344/DuCrj	10M + 10F	4 weeks dietary	0/0 0/10 300/0 3/10 30/10 300/10	No deaths, and no treatment related abnormalities in clinical signs, urine chemistry, or gross pathology, or upon urinalysis or ophthalmic examinations. Decr. in body weight, food consumption, heart weight and osmolality and increase in incidence of basophilic renal tubules, hypertrophy of juxtaglomerular cells for grps 300/0 and 300/10. Grps 300/0, 30/10 and 300/10 had an incr. in urine output, water intake, urea nitrogen, total chol. and atrophy of zona glomerulosa and a decr. in osmolality, erythrocytes, hematocrit and hemoglobin conc. and triglycerides. Grps 30/10 and 300/10 had an incr. in creatinine, ALP, LAP and inorganic phosphorus. M in grps 300/0 and 30/10 had an incr. in potassium as well as M and F in grp 300/10. F in grp 3/10 had an incr. in urine output, water intake, ALP, LAP and atrophy of the zona glomerulosa. F in grp 0/10 and 3/10 had a decr. in chloride.
Rat / Fischer 344/DuCrj	10M + 10F	13 weeks dietary	0/0 1/10 10/10 100/10	No deaths, and no abnormal signs. No toxicokinetic interactions occurred btw candesartan cilexetil and HCTZ. Grps 10/10 and 100/10 had an increase in basophilia of the renal tubules, calcification in the renal papilla, blood urea nitrogen, inorganic phosphorus and a decr. in calcium, total protein red blood cells, hemoglobin and hematocrit. The 100/10 grp had atrophy of the zona glomerulosa, urinary casts, white kidney patches, and an incr. in creatinine, and corpuscular volume.
Rat / Fischer 344/DuCrj	10M + 10F	13 weeks dietary	0/0 0/30 100/0 100/30	No deaths occurred and no abnormal signs. Toxic effects were seen in the 100/30 grp which included basophilic renal tubules and erosion/regeneration of the stomach. Decr. in body weight, urine osmolality and increases in water intake, urine volume, serum blood nitrogen and pathological changes noted above increased with concurrent administration. The 100/30 grp had an incr. in serum creatinine and inorganic phosphorus as well as shortening of prothrombin time and activated partial thromboplastin time.

Species/ Strain	No. Of Animals per Group	Duration and Route of Adminis- tration	Daily Dose candesartan cilexetil/HCTZ (mg/kg)	Results
Beagle	3M + 3F	4 weeks dietary	0/0 0/10 4/0 20/0 100/0 4/10 20/10 100/10	2 M were sacrificed after the 11 th and 24 th dose and 3 F died: 2 after the 10 th dose and 1 after the 14 th dose in the 100/10 (N=6) grp due to decreased locomotor activity, lack of food consumption and increase in plasma urea nitrogen concentration and creatinine. Increases in regeneration of renal tubules, hypertrophy of the juxtaglomerular cells, erosion or ulcer of the stomach were noted in most of the 100/10 grp and in some animals of the 20/10 group. Other abnormalities were decreases in osmolality, reticulocytes, chloride and potassium and increases in urea nitrogen, calcium, inorganic potassium, creatinine, erythrocytes, hematocrit and hemoglobin which were observed in various groups other than the control.
Beagle	3M + 3F	13 weeks dietary	0/0 0.8/10 4/10 20/10	2 F were sacrificed after the 31 st dose and 38 th dose in the 20/10 grp due to a decr. in movement and food consumption, hypothermia, paleness of conjunctival and oral mucosa and constipation. These F had an incr. in serum urea nitrogen, creatinine, inorganic phosphates and a decr. in sodium and chloride. The kidneys had tubular dilatation, severe regeneration of renal tubules, hypertrophy of juxtaglomerular cells and vacuolization and calcification in papilla. The stomach had erosion, mucosal hemorrhage and calcification and glands demonstrated atrophy. Decr. in urinary osmotic pressure for grp 20/10 and F of grps 0.8/10 and 4/10 as well as an incr. in sodium content for the latter. All other animals sacrificed on schedule showed no treatment change except for histological changes to kidneys.
Beagle	3M + 3F	13 weeks dietary	0/0 4/0 0/30 4/30	Treatment related deaths or severe toxic signs or symptoms did not occur in any animal. Hypertrophy of the juxtaglomerular cells occurred in the 4/0 and 4/30 animals. Increased urine vol. and decr. serum potassium occurred in the 0/30 and 4/30 grps.

Reproduction Studies

Reproductive studies were performed in rats, mice and rabbits. In rats, effects upon the maternal as well as upon the fetal body weight were recorded at 100/10 mg/kg/day and a minor skeletal effect was recorded upon the fetuses at 30/10 mg/kg/day with candesartan cilexetil/hydrochlorothiazide. The no observed adverse effect dose level in rats was 10/10 mg/kg of candesartan cilexetil and hydrochlorothiazide combination. The maternal toxicity was similar after monotherapy and the combination treatment. In mice, no maternal or fetal effects were seen at doses of up to 1000/10 mg/kg/day. In rabbits maternal toxicity with abortions and deaths was seen with doses from 1/10 mg/kg. The addition of hydrochlorothiazide did not significantly affect the outcome of the fetal development studies in any of the three species tested.

Mutagenicity

The studies performed show that the 1:2 mixture of candesartan cilexetil and hydrochlorothiazide is devoid of genotoxic activity in a range of *in vitro* studies in bacteria and in *in vivo* studies. These studies showed that candesartan cilexetil did not have a synergistic mutagenic effect when administered with hydrochlorothiazide. Taking into consideration all the studies conducted on the components and the combination it is concluded that the probability that the combination of candesartan cilexetil and hydrochlorothiazide being genotoxic to humans is extremely low.

Carcinogenicity

No carcinogenicity studies were carried out with the candesartan cilexetil/hydrochlorothiazide combination.

The carcinogenic potential of candesartan cilexetil was studied in rats after administration in the diet for 24 months. Dose levels were 100, 300 and 1000 mg/kg/day (50 male and 50 female rats per group). No alteration in tumour profile was observed. A two-year oral gavage study of candesartan cilexetil in mice was performed at daily dosages of 3, 10, 30 and 100 mg/kg/day. There was no alteration in the tumour profile.

There is no evidence that either candesartan cilexetil or hydrochlorothiazide are carcinogenic.

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PART III: CONSUMER INFORMATION

Fr Atacand[®] Plus

(candesartan cilexetil/hydrochlorothiazide tablets)

This leaflet is part III of a three-part "Product Monograph" published when ATACAND[®] PLUS was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about ATACAND PLUS. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

ATACAND PLUS is used to treat hypertension (high blood pressure).

You may not experience any signs of high blood pressure. If high blood pressure is not treated, damage may result to vital organs such as the heart or the kidneys. High blood pressure can lead to strokes, heart attacks, heart failure, kidney failure, or blindness. It is important to take ATACAND PLUS as directed by your doctor.

What it does:

ATACAND PLUS is the brand name for this drug, which is a combination of an angiotensin II AT₁ receptor blocker (candesartan cilexetil) and a diuretic (hydrochlorothiazide). Candesartan cilexetil and hydrochlorothiazide work together to lower high blood pressure.

- The candesartan cilexetil ingredient of ATACAND PLUS lowers blood pressure by specifically blocking a naturally occurring substance called angiotensin II. Blocking angiotensin II relaxes the arteries, letting the blood flow more freely, thereby lowering the blood pressure.
- The hydrochlorothiazide ingredient of ATACAND PLUS works by making your kidneys pass more water and salt.

When it should not be used:

You should not take ATACAND PLUS if:

- You are allergic to "non-medicinal" substances like food products, preservatives, or dyes, which may be present in ATACAND PLUS tablets (see What the nonmedicinal ingredients are).
- You have ever had a bad, unusual or allergic reaction to candesartan cilexetil or hydrochlorothiazide.
- You are not producing urine.

What the medicinal ingredient is:

Candesartan cilexetil and hydrochlorothiazide.

What the nonmedicinal ingredients are:

Most medicines contain more ingredients than just the active drug. These ingredients are needed to keep medicines in a form that you can swallow. Check with your doctor if you think you might be allergic to any of the following items (listed in alphabetical order): Calcium carboxymethylcellulose, hydroxypropyl cellulose, iron oxide, lactose, magnesium stearate, maize starch and polyethylene glycol.

What dosage forms it comes in:

ATACAND PLUS is available as tablets: 16 mg / 12.5 mg, 32 mg / 12.5 mg and 32 mg / 25 mg.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

ATACAND PLUS should not be used during pregnancy. If you discover that you are pregnant while taking ATACAND PLUS, stop the medication and please contact your physician.

Before you start ATACAND PLUS be sure you have told your doctor:

- **If you are pregnant, breast feeding or thinking about becoming pregnant.**
Taking ATACAND PLUS during pregnancy can cause injury and even death to your baby. This medicine should not be used during pregnancy. If you are planning to become pregnant while taking ATACAND PLUS, contact your doctor immediately. It is possible that ATACAND PLUS passes into breast milk. You should discuss with your doctor about taking ATACAND PLUS while breast feeding.
- About all health problems you have or have had in the past, including any heart, liver or kidney problems.
- If you have diabetes, gout or lupus erythematosus.
- If you are taking a diuretic therapy (water pills) or are on salt restrictive diet.
- If you are undergoing dialysis.
- If you are vomiting or have diarrhea.

The treatment of high blood pressure may lead to dizziness or weariness in some patients. Make sure you are not affected in this way before driving or operating machines.

If you are currently taking ATACAND PLUS and are going to have an operation, be sure to tell your doctor or dentist about your medication before you are given an anaesthetic.

INTERACTIONS WITH THIS MEDICATION

Before taking ATACAND PLUS be sure your doctor knows about all medicines you take, including ones you can buy without a prescription. If you visit more than one doctor make sure that each knows about all the medicines you are taking.

Drugs that may interact with ATACAND PLUS include:

- Other medicines used to lower blood pressure, including diuretics (water pills);
- Potassium-sparing diuretics, potassium supplements or potassium-containing salt substitutes;
- Lithium therapy;
- Digoxin;
- Medications to treat diabetes including insulin;
- Corticosteroids;
- Nonsteroidal anti-inflammatory agents (NSAIDs);
- Allopurinol (anti-gout treatment);
- Amantadine;
- Cytotoxic drugs (cancer therapy);
- Cholestyramine;
- Anticholinergic agents such as atropine and biperiden;
- Calcium or vitamin D supplements;
- Cyclosporine

Sedatives, tranquilizers, narcotics and alcohol may increase the blood-pressure lowering effect of ATACAND PLUS, so tell your physician or pharmacist if you are taking any of these.

PROPER USE OF THIS MEDICATION

Remember, you may not notice any signs of high blood pressure. **Therefore, it is important to take ATACAND PLUS even when you feel well.** A constant amount of drug is needed in your body to control your blood pressure. **Do not stop taking ATACAND PLUS on your own.**

Usual Dose:

Take ATACAND PLUS exactly as your doctor tells you. Do not miss doses or take extra doses, unless your doctor tells you. If you are not clear about the directions, ask your doctor or pharmacist.

The dosage of ATACAND PLUS is individualized.

ATACAND PLUS is not for initial therapy. You must first be stabilized on the individual components (candesartan cilexetil and hydrochlorothiazide) of ATACAND PLUS. If your dosage matches the dosages in ATACAND PLUS, your doctor may prescribe one tablet ATACAND PLUS taken once a day (instead of each component as a separate pill).

ATACAND PLUS is not for use in children under 18 years of age.

Try to take ATACAND PLUS with something you do regularly each day; for example, upon waking or at breakfast. This will help you remember each dose.

ATACAND PLUS may be taken with food or on an empty stomach, but it should be taken consistently the same way each day.

Swallow ATACAND PLUS with a glass of water.

To help you keep track of your doses, ATACAND PLUS comes in a Compliance Pack with days of the week printed on the back of the blister. Start with the tablet that matches the day of the week and continue taking them in order until they are all finished.

There are 14 days of labeled tablets in each blister, with one extra to make 15. All 15 tablets, including the one labeled "Take this tablet last", are exactly the same. Once you have finished the 14 labeled tablets take the one marked "Take this tablet last" before starting your next blister pack.

Remember to get a new prescription from your doctor or a refill from your pharmacy a few days before all your tablets are taken.

The package protects each tablet. When you first open the package, if you find any damage to the plastic seal or foil which exposes the tablet, ask your pharmacist to check the package.

Do not transfer ATACAND PLUS to other pill containers. To protect your ATACAND PLUS tablets, keep them in the original package.

Overdose:

If you take more ATACAND PLUS than you should, contact a doctor, the Regional Poison Control centre or pharmacist immediately.

Missed Dose:

If you miss a dose of ATACAND PLUS and remember within 12 hours, you should take your usual dose as soon as possible. Then go back to your regular schedule. But if it is more than 12 hours when you remember, do not take the missed dose. Just take the next dose on time.

Never take a double dose of ATACAND PLUS to make up for missed tablets. If you still have questions or concerns, check with your doctor or pharmacist to see what you should do.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Along with its effects on controlling blood pressure, ATACAND PLUS, like any medication, may cause side effects. These side effects are usually mild and should go away as your body gets used to ATACAND PLUS.

It is important that you keep your doctor informed if you suspect any side effects.

Effects that have been experienced include headache, throat infections, back pain and dizziness.

Side effects such as muscle pain, muscle weakness, muscle inflammation and rhabdomyolysis (a muscle-wasting disease), in rare cases leading to kidney failure, have been reported with the use of angiotensin II receptor blockers, the class of drugs to which a component of ATACAND PLUS belongs.

Medicines affect different people in different ways. Just because side effects have occurred in other patients does not mean you will get them. Discuss how you feel on ATACAND PLUS with your doctor and pharmacist. **Do not stop taking ATACAND PLUS on your own.**

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and seek emergency medical assistance
		Only if severe	In all cases	
Rare	Allergic reactions: swelling of the face, lips, tongue and/or throat; rash or other skin reactions			X
	Jaundice (yellow skin and/or eyes)			X
	Muscle pain that you cannot explain, muscle tenderness or weakness, generalized weakness		X	
	Dark/brown urine		X	

This is not a complete list of side effects. For any unexpected effects while taking ATACAND PLUS, contact your doctor or pharmacist.

HOW TO STORE IT

- Although the ATACAND PLUS tablets are protected in their package, it is best to keep the package at normal room temperature (15°C to 30°C) and in a dry place. Do not keep ATACAND PLUS in the bathroom.
- **Keep ATACAND PLUS out of sight and out of reach of children.** Never take medicine in front of small children as they will want to copy you.
- Do not keep or use ATACAND PLUS after the expiry date indicated on the package. Unused medicines, which you know you will no longer need, should be carefully discarded. You may wish to seek advice from your pharmacist.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada through the Canada Vigilance Program, collects information on serious and unexpected side effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Canada Vigilance:

By toll-free telephone: 866-234-2345
 By toll-free fax: 866-678-6789
 Online: www.healthcanada.gc.ca/medeffect
 By email: CanadaVigilance@hc-sc.gc.ca

By regular mail:
Canada Vigilance National Office
Marketed Health Products Safety and Effectiveness Information Bureau
Marketed Health Products Directorate
Health Products and Food Branch
Health Canada
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9

NOTE: Should you require information related to the management of the side effect, please contact your health care provider before notifying Canada Vigilance. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

All drugs can have both helpful and harmful effects. Both depend on the person and his or her health condition. This leaflet alerts you to some of the times you should call your doctor. Other situations which cannot be predicted may arise. Nothing in this leaflet should stop you from calling your doctor or pharmacist with any questions or concerns you have about ATACAND PLUS.

NOTE: This INFORMATION FOR THE CONSUMER leaflet provides you with the most current information at the time of printing. For the most current information, the Consumer Information Leaflet plus the full Product Monograph, prepared for health professionals can be found at:
www.astrazeneca.ca,
 or by contacting the sponsor, AstraZeneca Canada Inc. at:
 Customer Inquiries – 1 (800) 668-6000,
 Renseignements – 1 (800) 461-3787.

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