CILARIL PLUS

1. NAME OF THE MEDICINAL PRODUCT

CILARIL PLUS

2. QUALITATIVE AND QUANTITIVE COMPOSITION

Each CILARIL PLUS tablet contains 5 mg of cilazapril (as cilazapril monohydrate) and 12.5 mg hydrochlorothiazide.

For full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Tablets

CILARIL PLUS are round, biconvex, pale-brown film coated tablets with break-line on one side.

The use of CILARIL PLUS (cilazapril and hydrochlorothiazide) is contraindicated during pregnancy (see 4.3 CONTRAINDICATIONS). When used in pregnancy, angiotensin-converting enzyme (ACE) inhibitors can cause injury or even death of the developing fetus. Pregnant women should be informed of the potential hazards to the fetus and must not take CILARIL PLUS during pregnancy. Patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is detected, CILARIL PLUS should be discontinued as soon as possible and, if appropriate, alternative therapy should be started (see 4.6 Fertility, pregnancy and lactation).

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

CILARIL PLUS (cilazapril and hydrochlorothiazide) is indicated for:
Treatment of essential hypertension in patients who have been stabilized on the individual components given in the same proportions.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

Posology

Standard dosage for adults

The dosage of **CILARIL PLUS** is one tablet administered once daily. As food intake has no clinically significant influence on absorption, **CILARIL PLUS** can be administered before or after meals.
The dose should always be taken at about the same time of day.

Special dosage instructions

Renal insufficiency*:* When concomitant diuretic therapy is required in patients with severe renal impairment, a loop diuretic rather than a thiazide diuretic is preferred for use with cilazapril; therefore, for patients with severe renal dysfunction, **CILARIL PLUS** is not recommended (see 4.4 special warnings and precautions).

Prior diuretic therapy: In patients who are currently being treated with a diuretic for a reason other than hypertension, symptomatic hypotension occasionally can occur following the initial dose of cilazapril. To reduce the likelihood of hypotension, the diuretic should, if possible, be discontinued for 2 to 3 days prior to beginning therapy with cilazapril. If discontinuation of the diuretic is not possible, patients should be supervised for several hours after dosing, until blood pressure stabilizes.

Elderly**:** In clinical studies the efficacy and tolerability of cilazapril and hydrochlorothiazide, administered concomitantly, were similar in both elderly and younger hypersensitive patients.

Children: Safety and efficacy in children have not been established; therefore, **CILARIL PLUS** is not recommended for administration to children.

Missed Dose

Missed doses should not be replaced by double doses and medication should be resumed at the usual time.

Drug Discontinuation

- CILARIL PLUS should be promptly discontinued and appropriate therapy instituted without delay if angioedema occurs.
- Patients receiving cilazapril who develop jaundice or marked elevations of hepatic enzymes should discontinue cilazapril and receive appropriate medical follow-up.
- If increasing azotemia and oliguria occur during treatment of severe progressive renal disease the diuretic should be discontinued.
- If renal failure occurs, treatment should be discontinued.
- CILARIL PLUS should be withdrawn and appropriate treatment given if diagnosis of Acute Respiratory Distress Syndrome (ARDS) is suspected.

Angioneurotic edema has been reported in patients receiving cilazapril. CILARIL PLUS should be discontinued and appropriate therapy instituted without delay when involvement of the face, lips, tongue, glottis and/or larynx occurs.

4.3 CONTRAINDICATIONS

CILARIL PLUS (cilazapril and hydrochlorothiazide) is contraindicated in:

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see 6.1 List of Excipients.
- Patients with hereditary/idiopathic angioedema or a history of angioedema related to previous treatment with an angiotensin-converting enzyme (ACE) inhibitor (see 4.4 special warnings and precautions).
- Patients with ascites.
- Patients hypersensitive to thiazides and other sulfonamide-derived drugs, because of the hydrochlorothiazide component.
- Patients with anuria.
- Women who are pregnant, intend to become pregnant, or of childbearing potential who are not using adequate contraception (see 3 warnings and precautions box, see 4.6 Fertility, pregnancy and lactation and 4.8 undesirable effects).
- Breast-feeding (see 4.6 Fertility, pregnancy and lactation).
- Combination with aliskiren-containing drugs in patients with:
    - diabetes mellitus (type 1 or type 2) or
    - moderate to severe renal impairment (GFR < 60 ml/min/1.73m^2) (see 4.4 special warnings and precautions, 4.5 Serious Drug Interactionsand and drug interactions).
- Patients with hereditary problems of galactose intolerance, glucose-galactose malabsorption, or the Lapp lactase deficiency as CILARIL PLUS contains lactose (see 4.4 special warnings and precautions).
- Concomitant use with drug products containing a neprilysin inhibitor (e.g., sacubitril/valsartan). Do not administer CILARIL PLUS within 36 hours of switching to or from sacubitril/valsartan, a drug product containing a neprilysin inhibitor (see 4.4 special warnings and precautions and 4.5 drug interactions and Serious Drug Interactions).
- The safety and efficacy of CILARIL PLUS in congestive heart failure and renovascular hypertension have not been established and therefore, its use in these conditions is not recommended.
- The safety and efficacy of concomitant use of cilazapril with antihypertensive agents other than thiazide diuretics have not been established.

4.3 SPECIAL WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

Carcinogenesis and Mutagenesis

Non-melanoma skin cancer:

An increased risk of non-melanoma skin cancer (NMSC) [basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) of the skin] after hydrochlorothiazide therapy was reported in some epidemiological studies. The risk may be higher with increasing cumulative use (see 8.1 Adverse Reaction Overview). The photosensitizing action of hydrochlorothiazide may be a possible mechanism for NMSC.

Patients taking hydrochlorothiazide should be informed of the potential risk of NMSC. They should be advised to regularly check their skin for new lesions as well as changes to existing ones, and to promptly report any suspicious skin lesions. Patients should also be advised to limit exposure to sunlight, to avoid the use of indoor tanning equipment, and to use adequate protection (e.g. a broad spectrum sunscreen with a SPF of 30 or higher, clothing, and a hat) when exposed to sunlight or UV light to minimize the risk of skin cancer.

Alternatives to hydrochlorothiazide may be considered for patients who are at a particularly high risk for NMSC (e.g. light colored skin, known personal or family history of skin cancer, ongoing immunosuppressive therapy, etc.) (see 4.8 Adverse Reaction Overview).

Cardiovascular

Angioedema

Angioedema has been reported in patients treated with angiotensin-converting enzyme inhibitors including CILARIL PLUS (cilazapril and hydrochlorothiazide).

Angioedema has been associated with ACE inhibitors, with a reported incidence of 0.1-0.5%. Angioedema due to ACE inhibitors can present as recurrent episodes of facial swelling, which resolve on withdrawal, or as acute oropharyngeal edema and potentially life-threatening airway obstruction, which requires emergency treatment. Angioedema associated with laryngeal edema and/or shock may be fatal. A variant form is angioedema of the intestine, which tends to occur within the first 24-48 hours of treatment.

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at an increased risk of angioedema while receiving an ACE inhibitor (see 4.3 contraindications).

Concomitant use of ACE inhibitors with drug products containing a neprilysin inhibitor (e.g., sacubitril/valsartan) is contraindicated due to the increased risk of angioedema. Treatment with sacubitril/valsartan must not be initiated earlier than 36 hours after the last dose of cilazapril. Treatment with cilazapril must not be initiated earlier than 36 hours after the last dose of sacubitril/valsartan (see sections 4.3 CONTRAINDICATIONS, 4.5 Serious Drug Interactions and DRUG INTERACTIONS

Concomitant use of ACE inhibitors with mammalian target of rapamycin (mTOR) inhibitors such as sirolimus, everolimus, temsirolimus, or dipeptidyl peptidase IV (DPP-IV) inhibitors such as alogliptin, linagliptin, saxagliptin and sitagliptin may lead to an increased risk for angioedema (sudden difficulty in breathing or swallowing, swelling of face, eyes, lips, tongues and/or throat, hands or feet). Caution should be used when using mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) or DPP-IV inhibitors (e.g. alogliptin, linagliptin, saxagliptin and sitagliptin) concomitantly with ACE inhibitors (see 4.5 Drug-Drug Interactions).

Black-skinned patients of African descent also have a higher risk of angioedema.

Aortic Stenosis/Hypertrophic Cardiomyopathy
As with other ACE inhibitors, CILARIL PLUS should be used with caution in patients with obstructive cardiac disorders (e.g. mitral stenosis, aortic stenosis, hypertrophic cardiomyopathy), since cardiac output cannot increase to compensate for systemic vasodilation, and there is a risk of severe hypotension.

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.

Hypotension
Patients in whom cilazapril and diuretic are initiated simultaneously can develop symptomatic hypotension (see 4.5 drug interactions).

First-dose hypotension is most likely to occur in patients whose renin-angiotensin-aldosterone system is activated, such as in renovascular hypertension or other causes of renal hypoperfusion, sodium or volume depletion, or previous treatment with other vasodilators and in patients with dietary salt restriction, dialysis, diarrhea, or vomiting. These conditions can co-exist, particularly in severe heart failure.

Because of the potential fall in blood pressure in these patients, therapy with CILARIL PLUS should be started under very close medical supervision, and patients should be followed closely for the first two weeks of treatment.

Hypotension should be treated by placing the patient supine and volume expansion. CILARIL PLUS may be continued once the patient is volume replete but should be given at a lower dose or discontinued if hypotension persists.

Dual Blockade of the Renin-Angiotensin System (RAS)

There is evidence that co-administration of angiotensin-converting enzyme (ACE) inhibitors, such as the cilazapril component in CILARIL PLUS, or of angiotensin receptor antagonists (ARBs) with aliskiren increases the risk of hypotension, syncope, stroke, hyperkalemia and deterioration of renal function, including renal failure, in patients with diabetes mellitus (type 1 or type 2) and/or moderate to severe renal impairment (GFR < 60 ml/min/1.73m^2). Therefore, the use of CILARIL PLUS in combination with aliskiren-containing drugs is contraindicated in these patients (see 4.3 contraindications).

Further, co-administration of ACE inhibitors, including the cilazapril component of CILARIL PLUS, with other agents blocking the RAS, such as ARBs or aliskiren-containing drugs, is generally not recommended in other patients, since such treatment has been associated with an increased incidence of severe hypotension, renal failure, and hyperkalemia

Ear/Nose/Throat

Cough
A dry, persistent cough, which usually disappears only after withdrawal or lowering of the dose of CILARIL PLUS, has been reported. Such possibility should be considered as part of the differential diagnosis of the cough.

Endocrine and Metabolism

Thiazides may increase serum uric acid levels and may precipitate acute gout. CILARIL PLUS should be used with caution in patients with a history of gout.

Thiazides may decrease serum PBI levels without signs of thyroid disturbance.

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

Marked hypercalcemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests of parathyroid function.

Increases in cholesterol, triglyceride and glucose levels may be associated with thiazide diuretic therapy.

Diabetes
Hyperglycemia may occur with thiazide diuretics in diabetic patients. Dosage adjustments of insulin or oral hypoglycemic agents may be required. Latent diabetes mellitus may become manifest during thiazide therapy.

Administration of ACE inhibitors to patients with diabetes may potentiate the blood glucose-lowering effect of oral hypoglycemic agents or insulin, especially in patients with renal impairment. In such patients, glucose levels should be carefully monitored during initiation of treatment with CILARIL PLUS.

Hematologic

Neutropenia/Agranulocytosis
Thrombocytopenia, neutropenia and agranulocytosis have been caused by both ACE inhibitors and thiazides. Bone marrow depression has been caused by ACE inhibitors. Cases of leucopenia and neutropenia have rarely been reported in patients treated with ACE inhibitors. Periodic monitoring of white blood cell counts should be considered in patients with collagen vascular disease and renal disease such as systemic lupus erythematosus and scleroderma, or in patients receiving immunosuppressive therapy, especially when they also have impaired renal function.

Hydrochlorothiazide has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Autoimmune hemolytic anemia has been reported with thiazides.

Hepatic/Biliary/Pancreatic

Patients with Impaired Liver Function
Hepatitis (hepatocellular and/or cholestatic), jaundice, elevations of liver enzymes and/or serum bilirubin have occurred during therapy with cilazapril in patients with or without pre-existing liver abnormalities. In most cases the changes were reversed on discontinuation of the drug.

Cases of liver function disorders, such as increased values of liver function tests (transaminases, bilirubin, alkaline phosphatase, gamma GT) and cholestatic hepatitis have been reported.

There are no adequate studies in patients with cirrhosis and/or liver dysfunction. CILARIL PLUS should be used with particular caution in patients with pre-existing liver abnormalities. In such patients, baseline liver function tests should be obtained before administration of the drug and close monitoring of response and metabolic effects should apply.

In patients with liver cirrhosis (but without ascites) who require therapy for hypertension, CILARIL PLUS should be initiated with great caution because significant hypotension may occur. In patients with ascites, CILARIL PLUS is not recommended.

Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis, and (sometimes) death. The mechanism of this syndrome is not understood.

Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease and liver function should be monitored closely since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

Immune

Anaphylactoid Reactions During Membrane Exposure
Hemodialysis: Anaphylactoid reactions have been reported in patients dialyzed with high-flux membranes (e.g. polyacrylonitrile [PAN], AN 69) and treated concomitantly with an ACE inhibitor. Dialysis should be stopped immediately if symptoms such as nausea, abdominal cramps, burning, angioedema, shortness of breath and severe hypotension occur. Symptoms are not relieved by antihistamines. In these patients, consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agent.

Anaphylactoid Reactions During Low Density Lipoproteins (LDL) Apheresis
Patients receiving ACE inhibitors during LDL apheresis with dextran sulfate have experienced life-threatening anaphylactoid reactions. These reactions were avoided by temporarily withholding ACE inhibitor therapy prior to each apheresis.

Anaphylactoid Reactions During Desensitization
There have been reports of patients experiencing sustained life threatening anaphylactoid reactions while receiving ACE inhibitors during desensitizing treatment with Hymenoptera (bees, wasps) venom. In the same patients, these reactions have been avoided when ACE inhibitors were temporarily withheld for at least 24 hours, but they have reappeared upon inadvertent rechallenge.

Cilazapril use must be stopped before the start of desensitization therapy and must not be replaced by a beta-blocker.
Nitritoid Reactions – Gold

Nitritoid reactions (symptoms include facial flushing, nausea, vomiting, and symptomatic hypotension) have been reported rarely in patients on therapy with injectable gold (sodium aurothiomalate) and concomitant ACE inhibitor therapy including CILARIL PLUS (see 4.5 drug interactions).

Ophthalmologic

Choroidal effusion, Acute Myopia and Secondary Angle-Closure Glaucoma

Hydrochlorothiazide, a sulfonamide, can cause an idiosyncratic reaction, resulting in choroidal effusion, acute transient myopia and/or secondary acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity, blurred vision or ocular pain and typically occur within hours to weeks of drug initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss.

The primary treatment is to discontinue hydrochlorothiazide as rapidly as possible. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulphonamide or penicillin allergy.

Peri-Operative Considerations

Surgery/Anesthesia
In patients undergoing major surgery or during anesthesia with agents that produce hypotension, cilazapril blocks angiotensin II formation, secondary to compensatory renin release. This may result in arterial hypotension which can be corrected by volume expansion.

Renal

Azotemia
Azotemia may be precipitated or increased by hydrochlorothiazide. Cumulative effects of the drug may develop in patients with impaired renal function.

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 ACE inhibitors may produce increases in blood urea nitrogen and/or serum creatinine and has been associated with oliguria, progressive azotemia, and rarely, acute renal failure and/or death. Although these alterations are usually reversible upon discontinuation of cilazapril and/or diuretic therapy, cases of severe renal dysfunction and, rarely, acute renal failure have been reported. In susceptible patients, concomitant diuretic use may further increase risk.

Use of CILARIL PLUS should include appropriate assessment of renal function.

When treated with cilazapril, patients with renal artery stenosis have an increased risk of renal insufficiency, including acute renal failure. Therefore, caution should be exercised in these patients.

In the patient populations as described above, renal function should be monitored during the first weeks of therapy.

Reduced dosages may be required for patients with renal impairment depending on their creatinine clearance (see 4.2 Posology and method of administration).

Thiazides may not be appropriate diuretics for use in patients with renal impairment and are ineffective at creatinine clearance values of 30 ml/min or below (i.e. moderate or severe renal insufficiency).

The use of ACE inhibitors – including the cilazapril component of CILARIL PLUS– or ARBs with aliskiren-containing drugs is contraindicated in patients with moderate to severe renal impairment (GFR < 60 ml/min/1.73m^2). (See 4.3 contraindications and 4.5 drug interactions).

Respiratory

Acute Respiratory Toxicity
Very rare severe cases of acute respiratory toxicity, including acute respiratory distress syndrome (ARDS) have been reported after taking hydrochlorothiazide. Pulmonary edema typically develops within minutes to hours after hydrochlorothiazide intake. At the onset, symptoms include dyspnea, fever, pulmonary deterioration and hypotension. Hydrochlorothiazide should not be administered to patients who previously experienced ARDS following hydrochlorothiazide intake.

Sensitivity/Resistance

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

Exacerbation or activation of systemic lupus erythematosus has been reported in patients treated with hydrochlorothiazide.

Lactose Intolerance
Each CILARIL PLUS tablet contains 173mg lactose. Therefore, patients with hereditary galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine (see 4.3 contraindications).

Photosensitivity
Photosensitivity reactions have been reported with the use of thiazide diuretics. If photosensitivity reactions occur during treatment with hydrochlorothiazide-containing drugs, treatment should be stopped.

Serum Electrolytes
ACE inhibitors can cause hyperkalemia because they inhibit the release of aldosterone. The effect is usually not significant in patients with normal renal function. However, in patients with impaired renal function and/or in patients taking potassium supplements (including salt substitutes) or potassium-sparing diuretics, other drugs that may increase serum potassium (e.g. trimethoprim or co-trimoxazole (also known as trimethoprim/sulfamethoxazole)) and especially aldosterone antagonists or ARBs, hyperkalemia can occur. Potassium-sparing diuretics and ARBs should be used with caution in patients receiving ACE inhibitors, and serum potassium and renal function should be monitored (see 4.5 drug interactions).
In clinical trials, elevated serum potassium (greater than 5.5 mEq/L) was observed in approximately 0.7% of hypertensive patients receiving cilazapril alone. In most cases these were isolated values which resolved despite continued therapy, however, in one case the patient discontinued treatment. In clinical trials, hyperkalemia was rarely seen in patients using cilazapril and hydrochlorothiazide. Risk factors for the development of hyperkalemia may include renal insufficiency, diabetes mellitus, and the concomitant use of agents to treat hypokalemia (see 4.5 drug interactions , 4.8 undesireble

effects- Adverse Reaction Overview and Post-Market Adverse Reactions). Frequent monitoring of serum potassium may be advisable if these risk factors are present.

Thiazides increase potassium excretion and can cause hypokalemia. Hypokalemia may also occur in patients receiving cilazapril and hydrochlorothiazide, although to a lesser extent than that seen in patients receiving thiazide monotherapy. In patients receiving cilazapril and hydrochlorothiazide, the hypokalemic effect of hydrochlorothiazide alone is usually attenuated by the effect of cilazapril. Thiazides may decrease urinary calcium excretion and cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism.

Thiazides may also cause hyponatremia and dehydration. The risk of hyponatremia is greater in women, patients with hypokalemia or low sodium/solute intake, and in the elderly.

Electrolytes and renal function should be monitored in patients receiving cilazapril and hydrochlorothiazide.

4.5 DRUG INTERACTIONS

Serious Drug Interactions

- Combination with aliskiren-containing drugs in patients with:
  - diabetes mellitus (type 1 or type 2) or
  - moderate to severe renal impairment (GFR < 60 ml/min/1.73m^2) (see 4.4 special warnings and precautions and 4.5 drug interactions).
- Concomitant use with drug products containing a neprilysin inhibitor (e.g., sacubitril/valsartan) (see 7 WARNINGS AND PRECAUTIONS and 9.4 Drug-Drug Interactions).

Drug-Behavioural Interactions

A potentiation of orthostatic hypotension may occur when consuming alcohol while being on therapy with CILARIL PLUS. Therefore, alcohol should be avoided, especially with initiation of therapy.

Drug-Drug Interactions

The drugs listed in table 5 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 5 Established or Potential Drug-Drug Interactions

Proper Name	Ref.	Effect	Clinical comment
Agents increasing serum potassium (potassium sparing diuretics, trimethoprim-containing products, ciclosporin, heparin, potassium supplements or potassium-containing salt substitutes)	CT, C	Hyperkalemia may occur in some patients treated with CILARIL PLUS. Potassium sparing diuretics (e.g. spironolactone, triamterene, or amiloride), trimethoprim-containing products, ciclosporin, heparin, potassium supplements or potassium-containing salt substitutes may lead to significant increases in serum potassium impairment (see 5.1 PHARMACOLOGICAL PROPERTIES-Mechanism of Action and 4.4 SPECIAL WARNINGS AND PRECAUTIONS).	Therefore, the combination of cilazapril with agents increasing serum potassium (potassium sparing diuretics, trimethoprim-containing products, ciclosporin, heparin, potassium supplements or potassium-containing salt substitutes) is not recommended (see 4.4 SPECIAL WARNINGS AND PRECAUTIONS). If concomitant use is indicated severe hyperkalemia may occur. They should be used with caution and with frequent monitoring of serum potassium.
Alcohol, barbiturates, or narcotics	C	Potentiation of orthostatic hypotension may occur.	Avoid alcohol, barbiturates or narcotics, especially with initiation of therapy.
Amantadine		Simultaneous administration of amantadine and hydrochlorothiazide may increase possible adverse effects of amantadine.	Monitor the patient closely for adverse effects of amantadine and adjust the dosage of either medication as required.
Amphotericin B	T	Amphotericin B increases the risk of hypokalemia induced by thiazide diuretics	Monitor serum potassium level.
Antidiabetic agents (e.g. insulin and oral hypoglycemic agents)	CT*	Concomitant administration of ACE inhibitors and antidiabetic medicines (insulins, oral hypoglycemic agents) may cause an increased blood-glucose-lowering effect with risk of hypoglycemia. This phenomenon appeared to be more likely to occur during the first weeks of combined treatment and in patients with renal impairment.	Monitor glycemic control, supplement potassium if necessary, to maintain appropriate serum potassium levels, and adjust diabetes medications as required.

Proper Name	Ref.	Effect	Clinical comment
		Diabetes mellitus which has been latent may become manifest during thiazide administration. Thiazide-induced hyperglycemia may compromise blood sugar control. Depletion of serum potassium augments glucose intolerance. Concomitant use of ACE inhibitors with DPP-IV inhibitors (e.g. alogliptin, linagliptin, saxagliptin and sitagliptin) may lead to an increased risk for angioedema.	See 4.4 SPECIAL WARNINGS AND PRECAUTIONS
Antihypertensive drugs	CT	Hydrochlorothiazide may potentiate the action of other antihypertensive drugs (e.g. guanethidine, methyldopa, beta-blockers, vasodilators, calcium channel blockers, ACEI, ARB, and direct renin inhibitors). Patients concomitantly taking ACE inhibitors and diuretics, and especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy.	The possibility of hypotensive effects after the first dose of cilazapril can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with cilazapril.
Antineoplastic drugs, including cyclophosphamide and methotrexate	C	Concomitant use of thiazide diuretics may reduce renal excretion of cytotoxic agents and enhance their myelosuppressive effects.	Hematological status should be closely monitored in patients receiving this combination. Dose adjustment of cytotoxic agents may be required.
Bile acid sequestrants, e.g. cholestyramine, colestipol	CT	Bile acid sequestrants bind thiazide diuretics in the gut and impair gastrointestinal absorption by 43-85%. Administration of thiazide 4 hours after a bile acid sequestrant reduced absorption of hydrochlorothiazide by 30-35%.	Give thiazide 2-4 hours before or 6 hours after the bile acid sequestrant. Maintain a consistent sequence of administration. Monitor blood pressure, and increase dose of thiazide, if necessary.

Proper Name	Ref.	Effect	Clinical comment
Calcium and vitamin D supplements	C	Thiazides decrease renal excretion of calcium and increase calcium release from bone.	Monitor serum calcium, especially with concomitant use of high doses of calcium supplements. Dose reduction or withdrawal of calcium and/or vitamin D supplements may be necessary.
Carbamazepine	C	Carbamazepine may cause clinically significant hyponatremia. Concomitant use with thiazide diuretics may potentiate hyponatremia.	Monitor serum sodium levels. Use with caution.
Corticosteroids, and adrenocorticotropic hormone (ACTH)	T	Intensified electrolyte depletion, particularly hypokalemia, may occur.	Monitor serum potassium, and adjust medications, as required.
Ciclosporin		Simultaneous administration of ciclosporin and hydrochlorothiazide may increase the risk of developing hyperuricemia and gout-like complications.	Renal function, serum electrolytes, uric acid levels, and ciclosporin blood concentrations should be monitored. The clinical significance is unknown.
Digoxin	CT	No pharmacodynamic or pharmacokinetic interactions (and no increase in plasma digoxin concentrations) were observed when cilazapril therapy (5 mg once daily) was administered to healthy volunteers receiving digoxin (0.25 mg twice daily). Thiazide-induced electrolyte disturbances, i.e. hypokalemia, hypomagnesemia, can increase the risk of digoxin toxicity, which may lead to fatal arrhythmic events.	Concomitant administration of hydrochlorothiazide and digoxin requires caution. Since thiazide-induced hypokalemia may occur during therapy with CILARIL PLUS, which may increase the risk of arrhythmia associated with digoxin therapy, monitoring of potassium plasma levels is advised. Monitor electrolytes and digoxin levels closely. Supplement potassium or adjust doses of digoxin or thiazide, as required.

Proper Name	Ref.	Effect	Clinical comment
Drugs that alter GI motility, i.e., anti-cholinergic agents, such as atropine and prokinetic agents, such as metoclopramide, domperidone	CT, T	Bioavailability of thiazide diuretics may be increased by anticholinergic agents due to a decrease in gastrointestinal motility and gastric emptying. Conversely, prokinetic drugs may decrease the bioavailability of thiazide diuretics.	Dose adjustment of thiazide may be required.
Gold	C	Nitritoid reactions (symptoms include facial flushing, nausea, vomiting and hypotension) have been reported rarely in patients on therapy with injectable gold (sodium aurothiomalate) and concomitant ACE inhibitor therapy.	Use with caution when cilazapril and hydrochlorothiazide is co-administered with gold salts.
Gout medications (allopurinol, uricosurics, xanthine oxidase inhibitors)	T, RC	Thiazide-induced hyperuricemia may compromise control of gout by allopurinol and probenecid. The co-administration of hydrochlorothiazide and allopurinol may increase the incidence of hypersensitivity reactions to allopurinol.	Dosage adjustment of gout medications may be required.
Iodine containing contrast media		In case of dehydration induced by hydrochlorothiazide, there is an increased risk of acute renal impairment, in particular when larger doses of iodine containing contrast media are administered.	Before initiation of iodine containing contrast media administration, the patient should be advised about sufficient liquid intake and examined for typical symptoms of dehydration. Furthermore, it is recommended to check serum sodium level and renal function.
Lithium	CT	Reversible increases in serum lithium concentrations have been reported during concomitant administration of lithium with ACE inhibitors. Concomitant use of thiazide diuretics may increase the risk of lithium toxicity and enhance the already increased risk of lithium toxicity with ACE inhibitors.	Lithium generally should not be given with diuretics or ACE inhibitors. Use of cilazapril with lithium is not recommended, but if the combination proves necessary, careful and frequent monitoring of serum lithium levels should be performed.

Proper Name	Ref.	Effect	Clinical comment
		Lithium toxicity, including CNS symptoms, ECG changes and renal failure, has occurred in patients taking ACE inhibitors. Proposed mechanisms include decreased renal elimination of lithium due to decreased aldosterone secretion or decreased renal function.	
Medicinal products that could induce torsades de pointes		Hydrochlorothiazide may induce hypokalemia.	Due to the risk of hypokalemia, hydrochlorothiazide should be administered with caution when a patient is simultaneously being treated with medicinal products that could induce torsades de pointes such as: • Class Ia antiarrhythmics (e.g. quinidine, hydroquinidine, disopyramide) • Class III antiarrhythmics (e.g. amiodarone, sotalol, defetilide, ibutilide) • Some antipsychotics (e.g. thioridazine, chlorpromazine, trifluoperazine, sulpiride, tiapride, haloperidol, droperidol) Other medicinal products (e.g. bepridil, cisapride, diphemanil, halofantrine, ketanserin, pentamidine, terfenadine)

Proper Name	Ref.	Effect	Clinical comment
Nonsteroidal anti-inflammatory drugs (NSAID) including aspirin ≥ 3 g/day	CT	NSAID-related retention of sodium and water antagonises the diuretic and antihypertensive effects of thiazides. When ACE inhibitors, including CILARIL PLUS, are administered simultaneously with non-steroidal anti-inflammatory drugs (i.e. acetylsalicylic acid at anti-inflammatory dosage regimens, COX-2 inhibitors and non-selective NSAIDs), attenuation of the antihypertensive effect may occur. Concomitant use of ACE inhibitors, including CILARIL PLUS, 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 introduction of therapy with cilazapril (2.5 mg once daily) in hypertensive patients receiving indomethacin (50 mg twice daily) did not result in a reduction in blood pressure. However, the introduction of therapy with indomethacin (50 mg twice daily) in hypertensive patients receiving cilazapril (2.5 mg once daily) did not attenuate the blood pressure lowering effects of cilazapril. The interaction does not appear to occur in patients treated with cilazapril prior to the administration of a NSAID. There was no evidence of a pharmacokinetic interaction between cilazapril and indomethacin.	The combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated, and consideration should be given to monitoring for signs of worsening heart failure or renal function or loss of blood pressure control after initiation of concomitant therapy, and periodically thereafter.

Proper Name	Ref.	Effect	Clinical comment
		NSAID-induced inhibition of renal prostaglandins leading to decreases of renal blood flow, along with thiazide-induced decreases in GFR may lead to acute renal failure. Patients with heart failure may be at particular risk.	
Other antihypertensive agents	CT	An additive effect may be observed when CILARIL PLUS is administered in combination with other blood pressure-lowering agents (e.g. diuretics, beta- adrenergic blocking drugs). Agents affecting sympathetic activity (e.g. ganglionic blocking agents or adrenergic neuron blocking agents) should be used with caution. Sympathomimetics may reduce the antihypertensive effects of ACE inhibitors.	These drugs should be introduced at a low initial dosage and used with caution. Close monitoring of blood pressure is advised, and dose/regimen adjustment should be considered if necessary.
Pressor amines (e.g. norepinephrine)		Possible decreased response to pressor amines may occur.	The clinical significance of this effect is not sufficient to preclude their use.
Selective serotonin reuptake inhibitors (SSRIs, e.g. citalopram, escitalopram, sertraline)	T, C	Concomitant use with thiazide diuretics may potentiate hyponatremia.	Monitor serum sodium levels. Use with caution.
Skeletal muscle relaxants of the curare family, e.g. tubocurare	C	Thiazide drugs may increase the responsiveness of some skeletal muscle relaxants, such as curare derivatives	Non-depolarizing muscle relaxants should not be administered simultaneously, due to possible intensification and prolongation of the muscular relaxing effect.
Tetracycline	C	Increased toxicity has been reported when given with thiazides.	If signs indicative of toxicity are observed, dose reduction or discontinuation of one of both agents may be necessary.

Proper Name	Ref.	Effect	Clinical comment
Topiramate	CT	Additive hypokalemia. Possible thiazide-induced increase in topiramate serum concentrations.	Monitor serum potassium and topiramate levels. Use potassium supplements, or adjust topiramate dose as necessary.
Tricyclic antidepressants/antipsychotics/anesthetics/narcotics	C	Concomitant use of anesthetics during the course of general anesthesia, as well as tricyclic antidepressants and antipsychotics with ACE inhibitors may result in further reduction of blood pressure (see 4.4 SPECIAL WARNINGS AND PRECAUTIONS).	Close monitoring of blood pressure is advised, and dose/regimen adjustment should be considered if necessary.
Dual blockade of the Renin-Angiotensin-System (RAS) with ACE inhibitors, ARBs or aliskiren-containing drugs	CT	Dual Blockade of the Renin-Angiotensin-System (RAS) with ACE inhibitors, ARBs or aliskiren-containing drugs is contraindicated in patients with diabetes and/or renal impairment, and is generally not recommended in other patients, since such treatment has been associated with an increased incidence of severe hypotension, renal failure, and hyperkalemia.	See 4.3 CONTRAINDICATIONS, 4.5 Serious Drug Interactions and 4.4 SPECIAL WARNINGS AND PRECAUTIONS.
Sacubitril/valsartan	C	Concomitant use of ACE inhibitors with sacubitril/valsartan increases the risk of angioedema.	Concomitant use is contraindicated (see 4.3 CONTRAINDICATIONS, 4.5 Serious Drug Interactions and 4.4 SPECIAL WARNINGS AND PRECAUTIONS).
mTOR inhibitors	C, RCS	Concomitant use of ACE inhibitors with mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) may lead to an increased risk for angioedema.	See 4.4 SPECIAL WARNINGS AND PRECAUTIONS

Legend: C = Case Study; RCS = Retrospective Cohort Study; CT = Clinical Trial; T = Theoretical, CT*: Epidemiological studies.

4.6 SPECIAL POPULATIONS

FERTILITY, PREGNANCY AND LACTATION

Pregnant Women

ACE inhibitors can cause fetal and neonatal morbidity and mortality when administered to pregnant women. The use of CILARIL PLUS is contraindicated during pregnancy. Pregnant women should be informed of the potential hazards to the fetus and must not take CILARIL PLUS during pregnancy (see 4.3 CONTRAINDICATIONS). 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 CILARIL PLUS should be stopped immediately, and, if appropriate, alternative therapy should be started.

Fetal exposure to ACE inhibitors during the first trimester of pregnancy has been reported to be associated with an increased risk of malformations of the cardiovascular (atrial and/or ventricular septal defect, pulmonic stenosis, patent ductus arteriosus) and central nervous system (microcephaly, spina bifida) and of kidney malformations.

Exposure to ACE inhibitor therapy during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (hypotension, hyperkalemia, neonatal skull hypoplasia, intrauterine growth restriction, anuria, renal tubular dysplasia, reversible or irreversible renal failure and death). Oligohydramnios reported with the use of ACE inhibitors presumably resulted from decreased fetal renal function, associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Should exposure to ACE inhibitors have occurred from the second trimester of pregnancy, ultrasound examination of renal function and skull is recommended. Infants whose mothers have taken ACE inhibitors should be closely observed for hypotension.

Infants with a history of *in utero* exposure to ACE inhibitors 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.

Dialysis clearance was estimated to be 2.4 L/h for cilazapril and 2.2-2.8 L/h for cilazaprilat.

There is limited experience with hydrochlorothiazide during pregnancy. Thiazides cross the placenta. There have been reports of neonatal jaundice, thrombocytopenia and electrolyte imbalances after maternal use. Reductions in maternal blood volume could also adversely affect placental perfusion.

There is no experience concerning the extent of exposure in pregnancy during clinical trials.

Breast-feeding
Animal data show the presence of cilazaprilat in rat milk. However, no information is available regarding the safety of cilazapril during breast-feeding in humans. The presence of concentrations of ACE inhibitor have been reported in human milk. Use of ACE inhibitors is not recommended during breast-feeding. CILARIL PLUS must not be administered to nursing mothers (see 4.3 CONTRAINDICATIONS) and alternative treatments with better established safety profiles during breast-feeding are preferable. Furthermore, thiazides do appear in human milk.

In rats, it has been shown that after the oral administration of cilazapril, cilazaprilat is excreted in milk at concentrations resembling those in plasma.

OTHER SPECIAL POPULATIONS
Pediatrics (0-18 years)
No data is available.

Geriatrics
Although clinical experience has not identified differences in response between the elderly and younger patients, greater sensitivity of some older individuals cannot be ruled out (see 5 pharmacological properties and 4.2 posology and method of administration).

4.7 DRIVING AND OPERATING MACHINERY

Occasionally dizziness and fatigue may occur, especially when starting therapy (see 8 adverse reactions). Therefore, exercise caution when driving or operating a vehicle or potentially dangerous machinery.

4.8 UNDESIRABLE EFFECTS

Adverse Reaction Overview

Cilazapril and hydrochlorothiazide) has been evaluated for safety in 4,102 individuals (3,992 patients treated for essential hypertension and 110 normal volunteers enrolled in pharmacokinetic studies). In controlled clinical trials, 1,097 patients received the combination, cilazapril and hydrochlorothiazide, 225 received placebo, 437 received cilazapril alone and 340 received hydrochlorothiazide alone.

The most common adverse effects with cilazapril include dry cough, rash, hypotension, dizziness, fatigue, headache, and nausea, dyspepsia and other gastrointestinal disturbances. The most common adverse effects with hydrochlorothiazide are nausea, fatigue and dizziness.

The most serious adverse reactions reported included hypotension (0.3%) and angioedema (0.1%) (see 4.4 special warnings and precautions). The most frequent adverse reactions reported for the cilazapril/hydrochlorothiazide combination were headache (5.5%), dizziness (3.9%), fatigue (2.8%), coughing (2.6%), and somnolence (1.2%). Discontinuation of treatment due to adverse events occurred in 2.7% of patients.

Adverse events that have occurred have been those that were previously reported with cilazapril or hydrochlorothiazide when used separately for the treatment of hypertension.

Description of selected adverse events

Hypotension may occur when starting treatment or increasing dose, especially in at-risk patients (see 4.4 SPECIAL WARNINGS AND PRECAUTIONS). Symptoms of hypotension may include syncope, weakness, dizziness and visual impairment.

Renal impairment and acute renal failure are more likely in patients with severe heart failure, renal artery stenosis, pre-existing renal disorders or volume depletion (see 4.4 special warnings and precautions).

Hyperkalemia is most likely to occur in patients with renal impairment and those taking potassium sparing diuretics or potassium supplements.

The events of transient ischemic attack and ischemic stroke reported rarely in association with ACE inhibitors may be related to hypotension in patients with underlying cerebrovascular disease. Similarly, myocardial ischemia may be related to hypotension in patients with underlying ischemic heart disease.

Hypokalemia may occur in patients receiving CILARIL PLUS, although less commonly than in patients receiving thiazide monotherapy.

The risk of hyponatremia is greater in women, patients with hypokalemia or low sodium/solute intake, and the elderly.

Non-melanoma skin cancer
Some pharmaco-epidemiological studies have suggested a higher risk of squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) of the skin with increasing use of hydrochlorothiazide. A systematic review and meta-analysis suggested that, with important uncertainty, the use of hydrochlorothiazide for several years (>3 years) could lead to:

- 122 additional cases (95% CI, from 112 to 133 additional cases) of SCC per 1,000 treated patients compared with non-use of hydrochlorothiazide (meta-analysis of 3 observational studies);
- 31 additional cases (95% CI, from 24 to 37 additional cases) of BCC per 1,000 treated patients compared with non-use of hydrochlorothiazide (meta-analysis of 2 observational studies).

Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

See Table 3 for common adverse reactions (≥1%) reported by hypertensive patients treated with cilazapril and hydrochlorothiazide. The frequencies of ADRs from clinical trials for patients treated with cilazapril hydrochlorothiazide alone, and placebo alone in controlled clinical trials are also tabulated below. For comparison, adverse reactions tabulated for patients treated with cilazapril alone are as reported in the Product Monograph for cilazapril (cilazapril) tablets.

Table 3 Common Adverse Reactions (≥1%) reported by hypertensive patients treated with cilazapril and hydrochlorothiazide

Table Includes Frequencies for Hydrochlorothiazide Alone, and Placebo in Controlled Clinical Trials				
Body System/ Adverse Reaction	**Cilazapril (N=2586)**	**Cilazapril plus Hydro-chlorothiazide (N=1097)**	**Hydro-chlorothiazide (N=340)**	**Placebo (N=225)**
Gastrointestinal disorders				
Nausea	1.3%	1.0%	1.8%	0.4%
General disorders and administration site conditions				
Fatigue	2.1%	2.8%	2.1%	2.2%
Nervous system disorders				
Headache	5.1%	5.5%	6.5%	6.7%
Dizziness	3.0%	3.9%	3.5%	1.3%
Somnolence	0.5%	1.2%	-	0.9%
Renal and urinary disorders				
Micturition Frequency	0.2%	1.0%	0.6%	0.4%
Respiratory, thoracic and mediastinal disorders				
Coughing	1.8%	2.6%	0.3%	0.4%

Less Common Clinical Trial Adverse Reactions

Adverse reactions reported by patients treated with cilazapril and hydrochlorothiazide at a frequency <1% are as follows:

Cardiac disorders and Vascular disorders:

Palpitation (0.9%), Chest Pain (0.4%), Tachycardia (0.3%), Angina Pectoris (0.3%), Hypotension (0.3%), Postural Hypotension (0.1%), Edema Peripheral (0.3%), Edema Dependent (0.2%), Extrasystoles (0.2%), Myocardial Infarction (0.2%). Reported ≤0.1% were: Atrial Fibrillation, Bradycardia.

Gastrointestinal disorders:

Abdominal Pain (0.7%), Dyspepsia (0.7%), Diarrhea (0.5%), Flatulence (0.2%), Constipation (0.3%). Reported ≤0.1% were: Anorexia, Melena, Vomiting.

General disorders and administration site conditions:

Asthenia (0.6%), Malaise (0.3%), Hot Flushes (0.2%). Reported ≤0.1% were: Pain, Allergy, Face Edema, Fever, Weight Increase, Rigors, Hypothermia, Polyuria, Nocturia, Flushing, Peripheral

Ischemia, Cerebrovascular Disorder, Vasodilation, Vision Abnormal, Diplopia, Tinnitus, Ear Blockage, Purpura, Bleeding Time Increased, Gout, Thirst, Leukorrhea.

Musculoskeletal and connective tissue disorders

Back Pain (0.6%), Leg Cramps (0.6%), Arthralgia (0.3%), Myalgia (0.4%).

Nervous system disorders:

Hypoesthesia (0.3%), Paresthesia (0.3%), Vertigo (0.2%), Impotence (0.4%), Mouth Dry (0.3%), Sweating Increased (0.4%), Anxiety (0.2%), Depression (0.3%), Insomnia (0.1%), Nervousness (0.2%), Confusion (0.3%), Libido Decreased (0.2%). Reported ≤0.1% were: Libido Increased, Crying Abnormal, Paroniria, Dreaming Abnormal, Depersonalization, Neurosis.

Respiratory, thoracic and mediastinal disorders:

Rhinitis (0.7%), Upper Respiratory Tract Infection (0.1%), Pharyngitis (0.2%), Sinusitis (0.2%), Bronchitis (0.1%), Dyspnea (0.4%).

Skin and subcutaneous tissue disorders:

Rash (0.8%), Pruritus (0.4%). Reported ≤0.1% were: Dermatitis, Angioedema, Dry Skin.

Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

One thousand and ninety-seven patients received the combination test treatment. Clinically relevant laboratory abnormalities were reported most frequently for placebo. Laboratory abnormalities occurring in ≥1% of these patients were assessed as comparable with placebo except for the following parameters: low absolute neutrophil count, low potassium, low cholesterol-HDL, high glucose, high uric acid, high phosphorus and WBC in urine quantitative. Except for low cholesterol-HDL, all the above laboratory parameters were reported at equivalent or higher incidence for cilazapril alone or hydrochlorothiazide alone. Definitive evaluation of the effect of cilazapril and hydrochlorothiazide on cholesterol-HDL was not possible because controlled diet was not included in the design of this placebo-controlled trial.

Table 4 Overview Hematologic, Clinical Chemistry and Other Quantitative Data Clinical Trial Findings

	Abnormalities	Quantity
Hematology	Clinical relevant changes in neutrophil count	In 1.5% of patients (placebo: 1.3%)
	Clinical relevant changes in white blood cell count	In 0.3% of patients (placebo: 0.4%)
	Clinical relevant changes in low hemoglobin count	In 0.3% of patients (placebo: 0.9%)

Leukopenia and Neutropenia	Neutropenia	In 1% (11/1,097) of patients (These eleven patients had neutropenia with a neutrophil count <1,000. Ten of these patients had no clinical symptoms associated with these reported findings. In many of these cases, the findings were transient and believed to be due to laboratory handling problems. Some patients had a neutrophil count between 1,000 and 2,000 but none were associated with clinically serious adverse experiences.)
	Leukopenia	None of the patients evaluated during the study developed leukopenia (defined as a leukocyte count of <2,000).
Electrolytes	Decreased serum sodium (<130 mEq/L)	In 0.3% of patients (was not observed to be clinically relevant as two patients experienced no clinical symptoms and the third incidence of decreased serum sodium was caused by laboratory sample mishandling)
Liver Function Tests	High SGPT (clinical relevant change)	In 0.6% of patients
	Abnormalities	Quantity
	High SGOT (clinical relevant change)	In 0.4% of patients
Renal	High BUN (clinical relevant change)	In 0.4% of patients

Post-Market Adverse Reactions

The following adverse reactions have been seen in association with cilazapril and/or other ACE inhibitors alone, hydrochlorothiazide and/or other thiazide-type diuretics alone, and in those receiving combined therapy.

Frequency categories are as follows[1]:

Very common ≥ 1/10
Common ≥ 1/100 and < 1/10 Uncommon
< 1/100

[1]Estimates of frequency are based on the proportion of patients reporting each adverse reaction during cilazapril and hydrochlorothiazide clinical trials that included a total combined population of 1,097 patients. Adverse reactions that were not observed during cilazapril and hydrochlorothiazide clinical trials but have been reported in association with monotherapy with either component or with other ACE inhibitors or thiazide diuretics, or derived from post-marketing case reports, are classified as `uncommon' (<1/100). The category `uncommon' incorporates `rare' (≥1/10,000 and <1/1,000) and `very rare' (<1/10,000).

The frequency of adverse reactions attributable to cilazapril, occurring in patients receiving combination therapy (cilazapril+ hydrochlorothiazide), may differ from that seen in patients receiving cilazapril monotherapy. Reasons may include (i) differences between the target populations treated with cilazapril and hydrochlorothiazide and cilazapril, (ii) differences in cilazapril dose, and (iii) specific effects of combination therapy.

Adverse reactions to cilazapril

The most common adverse effects with cilazapril include dry cough, rash, hypotension, dizziness, fatigue, headache, and nausea, dyspepsia and other gastrointestinal disturbances.

Blood and lymphatic systems disorders

Uncommon: Neutropenia, agranulocytosis (especially in patients with renal failure and those with collagen vascular disorders such as systemic lupus erythematosus and scleroderma), thrombocytopenia, anemia

Cardiac disorders

Pronounced hypotension may occur at the start of therapy with ACE inhibitors, particularly in patients with heart failure and in sodium- or volume depleted patients. Myocardial infarction and stroke have been reported and may relate to severe falls in blood pressure in patients with ischemic heart disease or cerebrovascular disease. Other cardiovascular effects that have occurred include tachycardia, palpitations, and chest pain.

Gastrointestinal disorders

Common: Nausea
Uncommon: Pancreatitis (in some cases fatal)

General disorders and administration site conditions

Common: Fatigue

Hepatobiliary disorders
Uncommon: Abnormal liver function test (including transaminases, bilirubin, alkaline phosphatase, gamma GT), cholestatic hepatitis with or without necrosis.

Immune system disorders
Uncommon: Angioedema (may involve the face, lips, tongue, glottis, larynx or gastrointestinal tract, see 4.4 special warnings and precautions), anaphylaxis (see 4.4 special warnings and precautions), lupus-like syndrome (symptoms may include vasculitis, myalgia, arthralgia/arthritis, positive antinuclear antibodies, increased erythrocyte sedimentation rate, eosinophilia and leukocytosis).

Nervous system disorders
Common: Headache
Uncommon: Dysgeusia, transient ischemic attack, ischemic stroke (may be related in some cases to hypotension in patients with underlying cerebrovascular disease)

Renal and urinary disorders
Cases of acute renal failure have been reported in patients with severe heart failure, renal artery stenosis or renal disorders (see 4.4 special warnings and precautions).

Uncommon: Renal impairment, acute renal failure, blood creatinine increased, blood urea increased, hyperkalemia, hyponatremia (see 4.4 special warnings and precautions).

Respiratory, thoracic and mediastinal disorders
Common: Cough (sometimes severe)

Skin and subcutaneous tissue disorders
Uncommon: Toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, pemphigus, bullous pemphigoid, exfoliative dermatitis, dermatitis psoriasiform, psoriasis (exacerbation), lichen planus, urticaria, vasculitis, photosensitivity reactions, rash, alopecia, onycholysis,

Not known: pseudoporphyria

Vascular disorders
Common: Dizziness
Uncommon: Hypotension (sometimes severe, see 7 WARNINGS AND PRECAUTIONS)
Symptoms of hypotension may include syncope, weakness, dizziness and visual impairment.

Adverse reactions to hydrochlorothiazide

Blood and lymphatic disorders
Uncommon: Thrombocytopenia, hemolytic anemia, granulocytopenia

Cardiac disorders
Uncommon: Arrhythmia

Eye disorders
Uncommon: Lacrimation decreased, visual impairment

Unknown: Choroidal effusion, acute myopia, acute angle-closure glaucoma

Gastrointestinal disorders
Common: Nausea
Uncommon: Dry mouth, sialoadenitis, loss of appetite

General disorders and administration site conditions
Common: Fatigue

Hepatobiliary disorders
Uncommon: Cholestatic jaundice

Immune system disorders
Uncommon: Hypersensitivity (angioedema, anaphylaxis)

Metabolism and nutrition disorders
Uncommon: Hypokalemia, hyponatremia, hypochloremia, hypomagnesemia, hypercalcemia, hypocalciuria, hypovolemia/dehydration, metabolic alkalosis, hyperglycemia, hyperuricemia, gout, hypercholesterolemia (increased total, LDL and VLDL cholesterol) hypertriglyceridemia

Musculoskeletal and connective tissue disorders
Uncommon: Muscle cramp

Nervous system disorders
Common: Dizziness

Psychiatric disorders
Uncommon: Sleep disorder, depression

Renal and urinary disorders
Uncommon: Interstitial nephritis, renal impairment

Reproductive system and breast disorders
Uncommon: Sexual dysfunction

Respiratory, thoracic and mediastinal disorders
Uncommon: Acute interstitial pneumonitis, acute pulmonary edema, acute respiratory distress syndrome (ARDS) (see section 4.4 special warnings and precautions).

Skin and subcutaneous tissue disorders
Uncommon: Rash, photosensitivity, pseudoporphyria, cutaneous vasculitis

Vascular disorders
Uncommon: Hypotension

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il/
In addition, you can address “Unipharm Ltd.”.

4.9 OVERDOSAGE

Cilazapril:
Limited data are available with regard to overdosage in humans. Symptoms associated with overdosage of ACE inhibitors may include hypotension, which may be severe, circulatory shock, electrolyte disturbances including hyperkalemia and hyponatremia, renal impairment with metabolic acidosis, renal failure, hyperventilation, tachycardia, palpitations, bradycardia, dizziness, anxiety and cough.

The recommended treatment of overdosage is intravenous infusion of sodium chloride 9 mg/ml (0.9%) solution. If hypotension occurs, the patient should be placed in the shock position. If available, treatment with angiotensin II infusion and/or intravenous catecholamines may also be considered.
Specific therapy with angiotensinamide may be considered if conventional therapy is ineffective.

Pacemaker therapy is indicated for therapy-resistant bradycardia. Vital signs, serum electrolytes and creatinine concentrations should be monitored continuously.

Hemodialysis removes cilazapril and cilazaprilat from the general circulation to a limited extent.

Hydrochlorothiazide: The most common signs and symptoms observed are those caused by electrolyte depletion (hypokalemia, hypochloremia, hyponatremia) and dehydration resulting from excessive diuresis. If digitalis has also been administered, hypokalemia may accentuate cardiac arrhythmias.

5 PHARMACOLOGICAL PROPERTIES

5.1 Mechanism of Action

Cilazapril and hydrochlorothiazide combines the action of an angiotensin-converting enzyme (ACE) inhibitor, cilazapril, and a thiazide diuretic agent, hydrochlorothiazide for the treatment of hypertension. The anti-hypertensive effects of cilazapril and hydrochlorothiazide in combination are greater than the effect of either component administered alone resulting in a higher percentage of hypertensive patients responding satisfactorily to the combination.

Cilazapril: Cilazapril suppresses the renin-angiotensin-aldosterone system and thereby reduces both supine and standing systolic and diastolic blood pressures. Renin is an enzyme that is released by the kidneys into the circulation to stimulate the production of angiotensin I, an inactive decapeptide.
Angiotensin I is converted by angiotensin-converting enzyme (ACE) to angiotensin II, a potent vasoconstrictor. Angiotensin II also stimulates aldosterone secretion, leading to sodium and fluid retention. After absorption, cilazapril, a pro-drug, is hydrolyzed to cilazaprilat, the active metabolite, which prevents the conversion of angiotensin I to angiotensin II by inhibition of ACE. Following the administration of cilazapril, plasma ACE activity is inhibited more than 90% within two hours at therapeutic doses. Plasma renin activity (PRA) and angiotensin I concentrations are increased and angiotensin II concentrations and aldosterone secretion are decreased. The increase in PRA comes as a result of the loss of negative feedback on renin release caused by the reduction in angiotensin II. The decreased aldosterone secretion may lead to small increases in serum potassium along with sodium and fluid loss. In patients with normal renal function, serum

potassium usually remains within the normal range during cilazapril treatment. Mean serum potassium values increased by 0.02 mEq/L in patients with a normal baseline serum creatinine and by 0.11 mEq/L in patients with a raised serum creatinine. In patients concomitantly taking potassium-sparing diuretics, potassium levels may rise.

ACE is identical to kininase II. Therefore, cilazapril may interfere with the degradation of the vasodepressor peptide bradykinin. The role that this plays in the therapeutic effects of cilazapril is unknown.

Hydrochlorothiazide: Hydrochlorothiazide is a diuretic and antihypertensive which interferes with the renal tubular mechanism of electrolyte reabsorption. It increases excretion of sodium and chloride in approximately equivalent amounts. Natriuresis may be accompanied by some loss of potassium and bicarbonate. While this compound is predominately 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. The mechanism of its antihypertensive action is uncertain. Lowering of the sodium content of arteriolar smooth muscle cells and diminished response to norepinephrine have been postulated.

5.2 Pharmacodynamics

Cilazapril: The antihypertensive effect of cilazapril is usually apparent within the first hour after administration, with maximum effect observed between three and seven hours after dosing. Supine and standing heart rates remain unchanged. Reflex tachycardia has not been observed. Small, clinically insignificant alterations of heart rate may occur.

At recommended doses, the antihypertensive effect of cilazapril is maintained for up to 24 hours. In some patients, blood pressure reduction may diminish toward the end of the dosage interval. Blood pressure should be assessed after two to four weeks of therapy, and dosage adjusted if required. The antihypertensive effect of cilazapril is maintained during long-term therapy. No rapid increase in blood pressure has been observed after abrupt withdrawal of cilazapril.

The blood pressure-lowering effect of cilazapril in black patients may be less pronounced than in non- blacks. Racial differences in response are no longer evident when cilazapril is administered in combination with hydrochlorothiazide.
In hypertensive patients with moderate to severe renal impairment, the glomerular filtration rate and renal blood flow remained in general unchanged with cilazapril.

Hydrochlorothiazide: Use of hydrochlorothiazide increases plasma renin activity and aldosterone secretion resulting in a decrease in serum potassium. Cilazapril, by blocking the angiotensin/aldosterone axis attenuates the potassium loss associated with diuretic use. Concomitant use with hydrochlorothiazide results in a greater reduction of blood pressure by complementary mechanisms.

5.3 Pharmacokinetics

Cilazapril Absorption & Distribution: Cilazapril is well absorbed after oral administration and rapidly converted by ester cleavage to the active form, cilazaprilat. Peak plasma concentrations, and times to peak plasma concentrations for cilazapril and cilazaprilat following the oral administration of 0.5 to 5 mg cilazapril are given below.

Table 6 Peak Plasma Concentrations and Times to Peak Plasma Concentrations for Cilazapril and Cilazaprilat

Oral Dose	Cilazapril		Cilazaprilat	
	C_{max}	t_{max}	C_{max}	t_{max}
(mg)	(ng/mL)	(h)	(ng/mL)	(h)
0.5	17.0	1.1	5.4	1.8
1.0	33.9	1.1	12.4	1.8
2.5	82.7	1.1	37.7	1.9
5.0	182.0	1.0	94.2	1.6

Maximum plasma concentrations of cilazaprilat are reached within two hours after administration of cilazapril.

Maximum ACE inhibition is greater than 90% after 1 to 5 mg cilazapril. Maximum ACE inhibition is 70 to 80% after 0.5 mg cilazapril. Dose proportionality is observed following the administration of 1 to 5 mg cilazapril. Apparent non-proportionality is observed at 0.5 mg reflective of the binding to ACE. The higher doses of cilazapril are associated with longer duration of maximum ACE inhibition.

The absolute bioavailability of cilazaprilat after oral administration of cilazapril is 57% based on urinary recovery data. (The absolute bioavailability of cilazaprilat after oral administration of cilazaprilat is 19%.) Ingestion of food immediately before the administration of cilazapril reduces the average peak plasma concentration of cilazaprilat by 29%, delays the peak by one hour and reduces the bioavailability of cilazaprilat by 14%. These pharmacokinetic changes have little influence on plasma ACE inhibition.

Cilazapril Metabolism & Excretion: Cilazaprilat is eliminated unchanged by the kidneys. The total urinary recovery of cilazaprilat after intravenous administration of 2.5 mg is 91%. Total clearance is 12.3 L/h and renal clearance is 10.8 L/h. The total urinary recovery of cilazaprilat following the oral administration of 2.5 mg cilazapril is 52.6%.

Half-lives for the periods 1 to 4 hours and 1 to 7 days after the intravenous administration of 2.5 mg cilazaprilat are 0.90 and 46.2 hours respectively. These data suggest the saturable binding of cilazaprilat to ACE. The early elimination phase corresponds to the clearance of free drug. During the terminal elimination phase, almost all of the drug is bound to enzyme. Following the oral administration of 0.5, 1, 2.5 and 5 mg cilazapril, terminal elimination phase half-lives for cilazaprilat are 48.9, 39.8, 38.5 and
35.8 h respectively.

After multiple dose, daily administration of 2.5 mg cilazapril for 8 days, pharmacokinetic parameter values for intact cilazapril after the last dose are similar to the first dose. For cilazaprilat, peak plasma concentrations are achieved at the same time but are 30% higher after the last dose. Trough plasma concentrations and areas under the curve are 20% higher. The terminal elimination phase half-life after the last dose is 53.8 h. The effective half-life of accumulation for cilazaprilat is 8.9 h.

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

Hydrochlorothiazide Metabolism & Excretion: Hydrochlorothiazide is not metabolized but is eliminated rapidly by the kidney. When hydrochlorothiazide plasma levels have been followed for 24 hours, the plasma half-life has been observed to vary between 5.6-14.8 hours. At least 61% of the oral dose is eliminated unchanged within 24 hours.

Cilazapril-Hydrochlorothiazide Absorption: Concomitant administration of cilazapril and hydrochlorothiazide has little, or no effect on the bioavailability of either drug. The combination tablet is bioequivalent to concomitant administration of the separate entities.

Following oral administration of cilazapril and hydrochlorothiazide, hydrochlorothiazide is rapidly absorbed. Maximum plasma concentrations are consistently achieved within 2 hours post dosing. The bioavailability of hydrochlorothiazide after oral dose is about 65% based on urinary recovery. It is eliminated largely unchanged by the kidney, with a half-life of 7 to 11 hours.

AUC (area under the curve) values increase proportionally for cilazaprilat and hydrochlorothiazide with increasing doses of cilazapril and hydrochlorothiazide in the combination dosage form. The pharmacokinetic parameters of cilazaprilat are not altered in the presence of increasing doses of the hydrochlorothiazide component. Concomitant administration of cilazapril with hydrochlorothiazide has no effect on the bioavailability of either cilazaprilat, cilazapril or hydro-chlorothiazide. Administration of cilazapril and hydrochlorothiazide in the presence of food delays cilazaprilat T_{max} by 1.5 hours and reduces C_{max} by 24% and delays hydrochlorothiazide T_{max} by 1.4 hours and reduces C_{max} by 14% with no effect on overall bioavailability for either as assessed by AUC(0→24) values, indicating that there is an influence on rates but not on the extents of absorption.

Special Populations and Conditions

- **Geriatrics:** Following the administration of 1 mg cilazapril to healthy elderly and young volunteers, the elderly group experienced greater peak plasma concentrations of cilazaprilat and areas under the curve (39% and 25%, respectively) and lower total clearance and renal clearance (20% and 28%, respectively) than the younger volunteers.
- **Hepatic Insufficiency:**
  Hepatic Impairment: Following the administration of 1 mg cilazapril in patients with moderate to severe compensated liver cirrhosis, peak plasma concentrations of cilazapril and cilazaprilat are increased (57% and 28% respectively), attained 30 minutes and 45 minutes earlier, and total clearances are decreased (51% and 31% respectively), in comparison to healthy subjects. The renal clearance and early and terminal elimination phase half-lives of cilazaprilat are decreased 52%, 42% and 62% respectively.

- **Renal Insufficiency:** In patients with renal impairment, peak plasma concentrations of cilazaprilat, times to peak plasma concentrations, early elimination phase half-lives, areas under the curve and 24-hour plasma concentrations all increase as creatinine clearance decreases. The changes in these parameters are small for patients with creatinine clearances of 40 mL/min or more. Cilazaprilat clearance (total and renal) decreases in parallel with creatinine clearance. Cilazaprilat is not eliminated in patients with complete renal failure. Hemodialysis reduces concentrations of both cilazapril and cilazaprilat to a limited extent.
- **Ethnic origin:** ACE inhibitors are less effective as antihypertensives in black-skinned patients of African descent.

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS

Lactose anhydrous
Maize starch
Hydroxypropyl methylcellulose
Sodium stearyl fumarate
Opadry brown
Opadry white

6.2 SHELF LIFE

The expiry date of the product is indicated on the packaging materials.

Do not use CILARIL PLUS after the expiration date. The expiration date refers to the last day of the specified month.

6.3 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25˚C and protected from light.

6.4 NATURE AND CONTENTS OF CONTAINER

CILARIL PLUS is packed in ALU/ALU blister: 7,10, 14, 15, 28, 30 tablets.

Not all pack sizes may be marketed.

6.5 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

- The release of pharmaceuticals in the environment should be minimized. Medicines should not be disposed of via wastewater, and disposal through household waste should be avoided. Use established “collection systems” if available in your location.
- There are no special handling instructions necessary for this medicinal product.

7. MARKETING AUTHORIZATION HOLDER

Unipharm Ltd. P.O.B.21429 Tel-Aviv 61213

Manufacturer:

Unipharm Ltd. "Mevo Carmel" Industrial Park.

8. MARKETING REGISTRATION NUMBER(s)

135-95-31365-00

9. DATE OF REVISION OF THE TEXT

Revised in August 2023.