

PRODUCT MONOGRAPH

Pr **INHIBACE PLUS**[®]

cilazapril and hydrochlorothiazide

tablets 5 mg/12.5 mg

angiotensin-converting enzyme inhibitor / diuretic

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INHIBACE PLUS®

cilazapril and hydrochlorothiazide

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Non-medicinal Ingredients
Oral	Film-coated tablet (cilazapril/hydrochlorothiazide) 5 mg/12.5 mg	Cornstarch, hydroxypropyl methylcellulose, lactose, red iron oxide, sodium stearyl fumarate, talc, and titanium dioxide.

INDICATIONS AND CLINICAL USE

INHIBACE PLUS (cilazapril and hydrochlorothiazide) is indicated for treatment of mild to moderate essential hypertension in patients for whom combination therapy is appropriate.

In using INHIBACE PLUS consideration should be given to the risk of angioedema (see WARNINGS AND PRECAUTIONS).

Cilazapril should normally be used in those patients in whom treatment with diuretic or beta-blocker was found ineffective or has been associated with unacceptable adverse effects.

INHIBACE PLUS is not indicated for initial therapy. Patients in whom cilazapril and diuretic are initiated simultaneously can develop symptomatic hypotension (see WARNINGS AND PRECAUTIONS, DRUG INTERACTIONS, Drug-Drug Interactions).

Patients should be titrated on the individual drugs. If the fixed combination represents the dosage determined by this titration, the use of INHIBACE PLUS may be more convenient in the management of patients. If during maintenance therapy dosage adjustment is necessary, it is advisable to use individual drugs.

The safety and efficacy of INHIBACE 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.

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 WARNINGS AND PRECAUTIONS, ACTIONS AND CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

Pediatrics:

The safety and effectiveness of the use of INHIBACE PLUS in children have not been established. Therefore, use in this age group is not recommended.

CONTRAINDICATIONS

INHIBACE 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 the Dosage Forms, Composition and Packaging section of the product monograph.
- Patients with hereditary/idiopathic angioedema or a history of angioedema related to previous treatment with an angiotensin-converting enzyme (ACE) inhibitor (see WARNINGS AND PRECAUTIONS, General).
- 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 WARNINGS AND PRECAUTIONS, Special Populations, Pregnant Women and ADVERSE REACTIONS).
- Nursing women (see WARNINGS AND PRECAUTIONS, Special Populations, Nursing Women).
- Combination with aliskiren-containing drugs in patients with:
 - diabetes mellitus (type 1 or type 2) or
 - moderate to severe renal impairment ($GFR < 60 \text{ ml/min/1.73m}^2$) (see WARNINGS AND PRECAUTIONS, Dual Blockade of the Renin-Angiotensin System (RAS) and Renal, and DRUG INTERACTIONS, Drug-Drug Interactions: Dual Blockade of the Renin-Angiotensin-System (RAS) with ACE inhibitors, ARBs or aliskiren-containing drugs).
- Patients with hereditary problems of galactose intolerance, glucose-galactose malabsorption, or the Lapp lactase deficiency as INHIBACE PLUS[®] contains lactose (see WARNINGS AND PRECAUTIONS, Sensitivity/Resistance).
- Concomitant use with drug products containing a neprilysin inhibitor (e.g., sacubitril/valsartan). Do not administer INHIBACE PLUS within 36 hours of switching to or from sacubitril/valsartan, a drug product containing a neprilysin inhibitor (see WARNINGS AND PRECAUTIONS and DRUG INTERACTIONS).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

The use of INHIBACE PLUS (cilazapril and hydrochlorothiazide) is contraindicated during pregnancy (see 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 INHIBACE 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, INHIBACE PLUS should be discontinued as soon as possible and, if appropriate, alternative therapy should be started (see WARNINGS AND PRECAUTIONS).

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 ADVERSE REACTIONS, Post-Market Adverse Drug Reactions). The photosensitizing action of hydrochlorothiazide may be a possible mechanism for NMSC (see TOXICOLOGY, Carcinogenicity – Hydrochlorothiazide).

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 coloured skin, known personal or family history of skin cancer, ongoing immunosuppressive therapy, etc.) (see ADVERSE REACTIONS, Post-Market Adverse Drug Reactions).

Cardiovascular

Angioedema

Angioedema has been reported in patients treated with angiotensin-converting enzyme inhibitors including INHIBACE 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. If angioedema occurs, INHIBACE PLUS should be promptly discontinued and appropriate therapy instituted without delay. 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 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 CONTRAINDICATIONS and DRUG INTERACTIONS, Drug-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 DRUG INTERACTIONS, Drug-Drug Interactions).

Aortic Stenosis/Hypertrophic Cardiomyopathy

As with other ACE inhibitors, INHIBACE 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 should start treatment with INHIBACE PLUS only after they have been stabilized on each component given at the same dose as in the combined product. 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 INHIBACE PLUS should be started under very close medical supervision, and patients should be followed closely for the first two weeks of treatment. Patients at risk for hypotension should start treatment with INHIBACE PLUS with a low initial dose and careful titration. Similar caution should be taken for patients with angina pectoris or cerebrovascular disease, in whom hypotension can cause myocardial or cerebral ischemia.

Hypotension should be treated by placing the patient supine and volume expansion. INHIBACE 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 INHIBACE 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/1.73m²). Therefore, the use of INHIBACE PLUS in combination with aliskiren-containing drugs is contraindicated in these patients (see CONTRAINDICATIONS).

Further, co-administration of ACE inhibitors, including the cilazapril component of INHIBACE 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 INHIBACE 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. INHIBACE 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 INHIBACE PLUS.

Ethnicity

ACE inhibitors are less effective as antihypertensives in black-skinned patients of African descent. Black-skinned patients also have a higher risk of angioedema.

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

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. Patients receiving cilazapril who develop jaundice or marked elevations of hepatic enzymes should discontinue cilazapril and receive appropriate medical follow-up.

There are no adequate studies in patients with cirrhosis and/or liver dysfunction. INHIBACE 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, INHIBACE PLUS should be initiated with great caution because significant hypotension may occur. In patients with ascites, INHIBACE 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 INHIBACE PLUS (see DRUG INTERACTIONS, Drug-Drug Interactions).

Ophthalmologic

Acute Myopia and Secondary Angle-Closure Glaucoma

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

The primary treatment is to discontinue 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. If increasing azotemia and oliguria occur during treatment of severe progressive renal disease the diuretic should be discontinued.

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 INHIBACE 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. If renal failure occurs, treatment should be discontinued.

Reduced dosages may be required for patients with renal impairment depending on their creatinine clearance (see DOSAGE AND ADMINISTRATION, Dosage Adjustment in Patients with Renal Impairment).

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 INHIBACE PLUS – or ARBs with aliskiren-containing drugs is contraindicated in patients with moderate to severe renal impairment (GFR < 60 ml/min/1.73m²). (See CONTRAINDICATIONS and DRUG INTERACTIONS, Drug-Drug Interactions: Dual Blockade of the Renin-Angiotensin-System (RAS) with ACE inhibitors, ARBs or aliskiren-containing drugs).

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

INHIBACE PLUS tablets contain lactose. Therefore, patients with hereditary galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine (see 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 DRUG INTERACTIONS, Drug-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 INHIBACE PLUS. Risk factors for the development of hyperkalemia may include renal insufficiency, diabetes mellitus, and the concomitant use of agents to treat hypokalemia (see DRUG INTERACTIONS, Drug-Drug Interactions and 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 INHIBACE PLUS, although to a lesser extent than that seen in patients receiving thiazide monotherapy. In patients receiving INHIBACE PLUS, 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 INHIBACE PLUS.

Special Populations

Pregnant Women:

ACE inhibitors can cause fetal and neonatal morbidity and mortality when administered to pregnant women. The use of INHIBACE PLUS is contraindicated during pregnancy. Pregnant women should be informed of the potential hazards to the fetus and must not take INHIBACE PLUS during pregnancy (see 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 INHIBACE 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.

Animal Data:

In fertility and general reproduction performance testing in rats, dosing with 50 mg/kg/day of cilazapril resulted in greater implantation losses, less viable fetuses, smaller pups, and dilatation of the renal pelvis in the pups. No teratogenic effects and no adverse effects on postnatal pup development were observed in rats and cynomolgus monkeys during embryotoxicity testing. In the rats, however, at a dose of 400 mg/kg/day, renal cavitation was observed in the pups. In peri- and post-natal toxicity testing in rats, dosing with 50 mg/kg/day resulted in greater pup mortality, smaller pups, and delayed unfolding of the pinna. On administration of ¹⁴C-cilazapril to pregnant mice, rats and monkeys, radioactivity was measured in the fetuses.

No teratogenicity was observed when pregnant mice were treated orally (gavage) with up to 2,400 mg/kg/day (400 mg/kg/day CLZ and 2,000 mg/kg/day HCTZ) of a 1:5 cilazapril/hydrochlorothiazide combination from gestation days 6 through 15. In fetuses from dams treated with 300 mg/kg/day (50 mg/kg/day CLZ and 250 mg/kg/day HCTZ), there was an increased incidence of reduced frontal bone ossification and at 2,400 mg/kg/day (400 mg/kg/day CLZ and 2,000 mg/kg/day HCTZ) there was an increased incidence of reduced frontal and parietal bone ossification, misaligned sternbrae and sternbrae variants, as well as an increased incidence of dilated renal pelvises. All these effects are considered to represent developmental delays (see TOXICOLOGY, Table 12).

No teratogenicity was observed when pregnant rats were treated orally (gavage) with up to 37 mg/kg/day (6 mg/kg/day CLZ and 31 mg/kg/day HCTZ) of a 1:5

cilazapril/hydrochlorothiazide combination from gestation day 7 through 17. At 96 (16 mg/kg/day CLZ and 80 mg/kg/day HCTZ) and 240 mg/kg/day (40 mg/kg/day CLZ and 200 mg/kg/day HCTZ), fetal body weight was decreased resulting in decreased or absent ossification of a variety of bones in litters of dams given 240 mg/kg/day (see TOXICOLOGY, Table 12).

Nursing Women:

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. INHIBACE PLUS must not be administered to nursing mothers (see 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.

Ability to Drive and Use Machines

Occasionally dizziness and fatigue may occur, especially when starting therapy (see ADVERSE REACTIONS).

Pediatrics:

The safety and effectiveness of the use of INHIBACE PLUS in children have not been established. Therefore, use in this age group is not recommended.

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 INDICATIONS AND CLINICAL USE, ACTIONS AND CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

INHIBACE PLUS (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 serious adverse reactions reported included hypotension (0.3%) and angioedema (0.1%). 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.

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.

See table 1 for common adverse reactions ($\geq 1\%$) reported by hypertensive patients treated with INHIBACE PLUS. The frequencies of ADRs from clinical trials for patients treated with INHIBACE, 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 INHIBACE (cilazapril) tablets.

Table 1				
Common Adverse Reactions ($\geq 1\%$) Reported by Hypertensive Patients Treated with INHIBACE PLUS				
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)
Nervous System				
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%
Respiratory				
Coughing	1.8%	2.6%	0.3%	0.4%
Gastrointestinal				
Nausea	1.3%	1.0%	1.8%	0.4%
Miscellaneous				
Fatigue	2.1%	2.8%	2.1%	2.2%
Micturition Frequency	0.2%	1.0%	0.6%	0.4%

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

Adverse reactions reported by patients treated with INHIBACE PLUS at a frequency <1% are as follows:

Cardiovascular:

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 $\leq 0.1\%$ were: Atrial Fibrillation, Bradycardia.

Nervous System:

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 $\leq 0.1\%$ were: Libido Increased, Crying Abnormal, Paroniria, Dreaming Abnormal, Depersonalization, Neurosis.

Respiratory:

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

Gastrointestinal:

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

Dermatologic:

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

Musculoskeletal:

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

Miscellaneous:

Asthenia (0.6%), Malaise (0.3%), Hot Flushes (0.2%). Reported $\leq 0.1\%$ 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.

Abnormal Hematologic and Clinical Chemistry 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 $\geq 1\%$ 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 INHIBACE PLUS on cholesterol-HDL was not possible because controlled diet was not included in the design of this placebo-controlled trial.

Hematology: Clinically relevant changes in neutrophil count (1.5% of patients), white blood cell count (0.3% of patients) and low hemoglobin count (0.3% of patients) were observed. These abnormalities were comparably reported for placebo (1.3%, 0.4%, and 0.9%, respectively).

Liver Function Tests: Clinically relevant changes in the values associated with liver function occurred in up to 0.6% of patients as follows: High SGPT (0.6%) and high SGOT (0.4%).

Renal: Clinically relevant changes in renal function test results occurred in 0.4% of patients as follows: High BUN (0.4%).

Electrolytes: Decreased serum sodium (<130 mEq/L) reported in 0.3% of patients, upon further review 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.

Leukopenia and Neutropenia: Neutropenia was observed in 1% (11/1,097) of patients administered cilazapril/hydrochlorothiazide during the controlled clinical trials. 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. None of the patients evaluated during the study developed leukopenia (defined as a leukocyte count of $<2,000$).

Post-Market Adverse Drug 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 follows¹:

Very common $\geq 1/10$

Common $\geq 1/100$ and $< 1/10$

Uncommon $< 1/100$

¹ Estimates of frequency are based on the proportion of patients reporting each adverse reaction during INHIBACE PLUS clinical trials that included a total combined population of 1,097 patients. Adverse reactions that were not observed during INHIBACE PLUS 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' ($\geq 1/10,000$ 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 INHIBACE PLUS and INHIBACE, (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

Blood disorders have been reported with ACE Inhibitors and include neutropenia and agranulocytosis (especially in patients with renal failure and those with collagen vascular disorders such as systemic lupus erythematosus and scleroderma), thrombocytopenia, and hemolytic anemia.

Uncommon: Neutropenia, agranulocytosis, 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.

Uncommon: Myocardial infarction, tachycardia, palpitations, angina pectoris

Vascular disorders

Common: Dizziness

Uncommon: Hypotension (sometimes severe, see WARNINGS AND PRECAUTIONS)

Symptoms of hypotension may include syncope, weakness, dizziness and visual impairment.

Respiratory, thoracic and mediastinal disorders

Common: Cough (sometimes severe)

Gastrointestinal disorders

As for other ACE inhibitors, isolated cases of pancreatitis, in some cases fatal, have been reported in patients treated with INHIBACE PLUS.

Common: Nausea

Uncommon: Pancreatitis

Hepatobiliary disorders

Single cases of liver function disorders, such as increased liver function tests (transaminases, bilirubin, alkaline phosphatase, gamma GT) and cholestatic hepatitis with or without necrosis, have been reported (see WARNINGS AND PRECAUTIONS).

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

Immune system disorders

As with other ACE inhibitors, angioneurotic edema has been reported in patients receiving cilazapril (see WARNINGS AND PRECAUTIONS). Since this syndrome can be associated with laryngeal edema, cilazapril should be discontinued and appropriate therapy instituted without delay when involvement of the face, lips, tongue, glottis and/or larynx occurs.

Uncommon: Angioedema (may involve the face, lips, tongue, glottis, larynx or gastrointestinal tract, see WARNINGS AND PRECAUTIONS), anaphylaxis (see 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)

Skin and subcutaneous tissue disorders

Skin rashes (including pemphigus, Stevens-Johnson syndrome, erythema multiforme and toxic epidermal necrolysis) may occur; photosensitivity, alopecia, and other hypersensitivity reactions have also been reported. Other reported skin reactions include vasculitis, erythema multiforme and pseudoporphyria.

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

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 WARNINGS AND PRECAUTIONS: Renal Impairment).

Uncommon: Renal impairment, acute renal failure, blood creatinine increased, blood urea increased, hyperkalemia, hyponatremia (see WARNINGS AND PRECAUTIONS, Renal).

General disorders and administration site conditions

Common: Fatigue

Adverse reactions to hydrochlorothiazide

Blood and lymphatic disorders

Uncommon: Thrombocytopenia, hemolytic anemia, granulocytopenia

Cardiac disorders

Uncommon: Arrhythmia

Eye disorders

Uncommon: Lacrimation decreased, visual impairment

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

Skin and subcutaneous tissue disorders

Uncommon: Rash, photosensitivity, pseudoporphyria, cutaneous vasculitis

Respiratory, thoracic and mediastinal disorders

Uncommon: Acute interstitial pneumonitis, acute pulmonary edema

Vascular disorders

Uncommon: Hypotension

Description of selected adverse events

Hypotension may occur when starting treatment or increasing dose, especially in at-risk patients (see 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 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 INHIBACE 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 pharmacoepidemiological 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 undertaken by Health Canada 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).

DRUG INTERACTIONS

Drug-Drug Interactions

Table 2 Established or Potential Drug-Drug Interactions

Proper Name	Ref.	Effect	Clinical comment
Agents increasing serum potassium (potassium sparing diuretics, trimethoprim-containing products, cyclosporine, heparin, potassium supplements or potassium-containing salt substitutes)	CT, C	Hyperkalemia may occur in some patients treated with INHIBACE PLUS. Potassium sparing diuretics (e.g. spironolactone, triamterene, or amiloride), trimethoprim-containing products, cyclosporine, heparin, potassium supplements or potassium-containing salt substitutes may lead to significant increases in serum potassium impairment (see ACTION AND CLINICAL PHARMACOLOGY and WARNINGS AND PRECAUTIONS).	Therefore, the combination of cilazapril with agents increasing serum potassium (potassium sparing diuretics, trimethoprim-containing products, cyclosporine, heparin, potassium supplements or potassium-containing salt substitutes) is not recommended (see 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	Potential 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.	
Amphotericin B	T	Amphotericin B increases the risk of hypokalemia induced by thiazide diuretics	Monitor serum potassium level.

Proper Name	Ref.	Effect	Clinical comment
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.
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 adrenocorticotrophic hormone (ACTH)	T	Intensified electrolyte depletion, particularly hypokalemia, may occur.	Monitor serum potassium, and adjust medications, as required.
Cyclosporine		Simultaneous administration of cyclosporine and hydrochlorothiazide may increase the risk of developing hyperuricemia and gout-like complications.	

Proper Name	Ref.	Effect	Clinical comment
Digoxin	CT	<p>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).</p> <p>Thiazide-induced electrolyte disturbances, i.e. hypokalemia, hypomagnesemia, can increase the risk of digoxin toxicity, which may lead to fatal arrhythmic events.</p>	<p>Concomitant administration of hydrochlorothiazide and digoxin requires caution. Since thiazide-induced hypokalemia may occur during therapy with INHIBACE 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.</p>
Drugs that alter GI motility, i.e., anti-cholinergic agents, such as atropine and prokinetic agents, such as metoclopramide, domperidone	CT, T	<p>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.</p>	<p>Dose adjustment of thiazide may be required.</p>
Gold	C	<p>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.</p>	<p>Use with caution when INHIBACE PLUS is co-administered with gold salts.</p>
Gout medications (allopurinol, uricosurics, xanthine oxidase inhibitors)	T, RC	<p>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.</p>	<p>Dosage adjustment of gout medications may be required.</p>

Proper Name	Ref.	Effect	Clinical comment
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.	
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 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.	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.
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: <ul style="list-style-type: none"> • Class Ia antiarrhythmics (e.g. quinidine, hydroquinidine, disopyramide)

Proper Name	Ref.	Effect	Clinical comment
			<ul style="list-style-type: none"> • Class III antiarrhythmics (e.g. amiodarone, sotalol, defetilide, ibutilide) • Some antipsychotics (e.g. thioridazine, chlorpromazine, trifluoperazine, sulpiride, tiapride, haloperidol, droperidol) <p>Other medicinal products (e.g. bepridil, cisapride, diphemanil, halofantrine, ketanserin, pentamidine, terfenadine)</p>
<p>Nonsteroidal anti-inflammatory drugs (NSAID) including aspirin ≥ 3 g/day</p>	<p>CT</p>	<p>NSAID-related retention of sodium and water antagonises the diuretic and antihypertensive effects of thiazides.</p> <p>When ACE inhibitors, including INHIBACE 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 INHIBACE 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.</p>	<p>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.</p>

Proper Name	Ref.	Effect	Clinical comment
		<p>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.</p> <p>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.</p>	
Other antihypertensive agents	CT	<p>An additive effect may be observed when INHIBACE PLUS is administered in combination with other blood pressure-lowering agents (e.g. diuretics, beta-adrenergic blocking drugs).</p> <p>Agents affecting sympathetic activity (e.g. ganglionic blocking agents or adrenergic neuron blocking agents) should be used with caution.</p>	<p>These drugs should be introduced at a low initial dosage and used with caution.</p> <p>Close monitoring of blood pressure is advised, and dose/regimen adjustment should be considered if necessary.</p>

Proper Name	Ref.	Effect	Clinical comment
		Sympathomimetics may reduce the antihypertensive effects of ACE inhibitors.	
Pressor amines (e.g. norepinephrine)		Possible decreased response to pressor amines may occur but not sufficiently 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. tubocurarine	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.	
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 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	See CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS, Dual Blockade of the Renin- Angiotensin-System (RAS).

Proper Name	Ref.	Effect	Clinical comment
		associated with an increased incidence of severe hypotension, renal failure, and hyperkalemia.	
Sacubitril/valsartan	C	Concomitant use of ACE inhibitors with sacubitril/valsartan increases the risk of angioedema.	Concomitant use is contraindicated (see CONTRAINDICATIONS and 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 WARNINGS AND PRECAUTIONS , Cardiovascular, Angioedema

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

DOSAGE AND ADMINISTRATION

Dosing Considerations

Dosage must be individualized. The fixed combination is not for initial therapy. The dose of INHIBACE PLUS (cilazapril and hydrochlorothiazide) should be determined by titration of the individual components.

Once the patient has been successfully titrated with the individual components as described below, INHIBACE PLUS may be substituted if the titrated doses and dosing schedule can be achieved by the fixed combination (see INDICATIONS AND CLINICAL USE and WARNINGS AND PRECAUTIONS). In some patients a twice daily administration may be required.

The tablets must not be chewed or crushed and should always be swallowed with a glass of water.

Recommended Dose and Dosage Adjustment

Initial therapy with cilazapril

Monotherapy: The recommended initial dose of INHIBACE is 2.5 mg once daily. Dosage should be adjusted according to the blood pressure response, generally at intervals of at least two weeks. The usual dose range for INHIBACE is 2.5 to 5 mg once daily. Minimal additional blood pressure lowering effects were achieved with a dose of 10 mg daily. A dose of 10 mg should not be exceeded.

In most patients, the antihypertensive effect of INHIBACE is maintained with a once daily dosing regimen. In some patients treated once daily, the antihypertensive effect may diminish toward the end of the dosing interval. This can be evaluated by measuring blood pressure just prior to dosing to determine whether satisfactory control is being maintained for 24 hours. If it is not, either twice daily administration with the same total daily dose, or an increase in dose should be considered. If blood pressure is not adequately controlled with INHIBACE alone a non-potassium-sparing diuretic may be administered concomitantly. After the addition of a diuretic, it may be possible to reduce the dose of INHIBACE.

Concomitant Diuretic Therapy: In patients receiving diuretics, INHIBACE therapy should be initiated with caution, since they are usually volume depleted and more likely to experience hypotension following ACE inhibition. Whenever possible, all diuretics should be discontinued two to three days prior to the administration of INHIBACE to reduce the likelihood of hypotension (see WARNINGS AND PRECAUTIONS). If this is not possible because of the patient's condition, INHIBACE should be started at 0.5 mg once daily and the blood pressure closely monitored after the first dose until stabilized. Thereafter, the dose should be adjusted according to individual response.

Dosage in Elderly Patients (Over 65 Years): INHIBACE treatment should be initiated with 1.25 mg (half of a 2.5 mg tablet) once daily or less, depending on the patient's volume status and general condition. Thereafter, the dose of INHIBACE must be adjusted according to individual response.

Dosage Adjustment in Renal Impairment: See Table 3 for dose schedules recommended in patients with renal impairment.

Table 3 Dosage Adjustment in Renal Impairment		
Creatinine Clearance	Initial Dose Of INHIBACE	Maximal Dose Of INHIBACE
> 40 mL/min	1 mg once daily	5 mg once daily
10-40 mL/min	0.5 mg once daily	2.5 mg once daily
< 10 mL/min	Not recommended.	

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 (creatinine clearance < 10 mL/min) INHIBACE PLUS is not recommended.

Dosage Adjustment in Hepatic Impairment: Should patients with liver cirrhosis require treatment with INHIBACE, treatment should be initiated with caution at a dose of 0.5 mg once daily or less as significant hypotension may occur (see WARNINGS AND PRECAUTIONS).

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.

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

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

INHIBACE PLUS (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.

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.

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 4 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 INHIBACE PLUS, 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 $AUC(0\rightarrow 24)$ 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.

STORAGE AND STABILITY

Store 15-30°C. Keep container tightly closed.

SPECIAL HANDLING INSTRUCTIONS

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.

DOSAGE FORMS, COMPOSITION AND PACKAGING

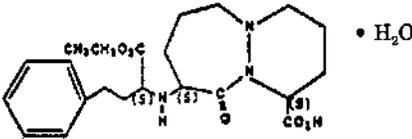
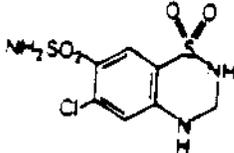
INHIBACE PLUS 5 mg/12.5 mg film-coated tablets contain 5 mg cilazapril, as cilazapril monohydrate and 12.5 mg hydrochlorothiazide.

Non-medicinal ingredients: cornstarch, hydroxypropyl methylcellulose, lactose, red iron oxide, sodium stearyl fumarate, talc, and titanium dioxide.

INHIBACE PLUS (cilazapril and hydrochlorothiazide) is available as film-coated tablets containing: 5 mg cilazapril and 12.5 mg hydrochlorothiazide available in blister packages of 28 tablets. The tablets are pale red, oval shaped single-scored biconvex imprinted CIL + on the top half and 5 + 12,5 on the bottom half of one side of the tablet.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance:	Cilazapril Monohydrate	Hydrochlorothiazide
Proper Names:	cilazapril monohydrate	hydrochlorothiazide
Chemical Names:	9 (s)-[1(s)-(ethoxycarbonyl)-3-phenylpropylamino]-octahydro-10-oxo-6H-pyridazo [1,2-a] [1,2] diazepine-1(s)-carboxylic acid monohydrate	6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1dioxide
Molecular Formulas:	$C_{22}H_{31}N_3O_5 \cdot H_2O$	$C_7H_8ClN_3O_4S_2$
Structural Formula		
Molecular Weights:	435.52	297.72
Physical Forms:	Cilazapril is a white to off-white crystalline powder	Hydrochlorothiazide is a white or practically white crystalline compound.
Solubility:	Water (25°C) 0.5 g/100 mL	Practically insoluble in water
pka1, pka2:	3.3, 6.4	7.9, 9.2
pH (1%) suspension):	4.9	
Partition Co-efficient:	0.8 (octanol-pH 7.4 buffer 22°C)	
Melting Point:	98°C with decomposition	131°C with decomposition

DETAILED PHARMACOLOGY

Cilazapril Pharmacology: In *in vitro* studies, using hippurylhistidylleucine as substrate, cilazaprilat, the active metabolite of cilazapril, inhibited the activity of ACE from rabbit lung (IC_{50} 0.97-1.93 nM), hog lung (IC_{50} 2.83 nM), human lung (IC_{50} 1.39 nM), and human plasma (IC_{50} 0.61 nM). Cilazaprilat (20 μ M) did not have any effect on a number of other porcine, bovine, or human enzymes except *E. coli* dipeptidyl carboxypeptidase.

In *ex vivo* studies, oral administration of 0.1 and 0.25 mg/kg cilazapril to rats inhibited plasma ACE activity by 76% and 96% respectively and 0.3-3 mg/kg significantly inhibited tissue ACE activity in a number of arteries and veins.

In vivo, the dose of cilazapril and/or cilazaprilat required to reduce the angiotensin pressor response by 50% are summarized in Table 5 below.

Animal Model	Cilazapril Activity	Cilazaprilat Activity
Conscious normotensive rats	ED ₅₀ 0.02 mg/kg p.o. (at 60 min)	-
Anesthetized SHAD (unilaterally adrenalectomized and contralaterally adrenal demedullated SHR) rats	ED ₅₀ 0.44 μ mol/kg i.v.	ED ₅₀ 0.06 μ mol/kg i.v.
2-kidney-1-clip Goldblatt renal hypertensive rats	ED ₅₀ 0.043 mg/kg i.v.	ED ₅₀ 0.006 mg/kg i.v.
Anesthetized normotensive dogs	ED ₅₀ 0.035 mg/kg i.v. (0.084 μ mol/kg)	-

In the anesthetized SHAD rats 0.06 μ mol/kg i.v. cilazaprilat potentiated the bradykinin induced vasodepressor response.

The antihypertensive activity of cilazapril was assessed in a number of experimental animal models. In spontaneously hypertensive rats (SHR), single oral doses of 10 and 30 mg/kg cilazapril reduced systolic blood pressure for longer than six hours. Repeated daily dosing with oral doses of 10 and 30 mg/kg cilazapril demonstrated 24-hour activity and at the higher dose, antihypertensive effect became maximum after one week. When administered twice daily, the lowest oral dose of cilazapril that reduced systolic blood pressure was 1 mg/kg. Dose dependent decreases in systolic blood pressure were observed between oral doses of 1 and 10 mg/kg twice daily. No further increase in effect was observed with an oral dose of 30 mg/kg twice daily.

Intravenous administration of up to 10 mg/kg of either cilazapril or cilazaprilat to conscious SHR evoked only small reductions in blood pressure. The reason for this disparity with the oral dosing data in the same animal model is unclear.

Following the oral administration of 10 mg/kg cilazapril, the maximum decrease in systolic arterial pressure observed in conscious renal hypertensive hypovolemic dogs was approximately double that observed in normovolemic dogs. In the hypovolemic dogs, the systolic blood pressure fell significantly within 30 minutes of the first dose. The effect persisted for 6 hours. Maximum decrease in systolic arterial pressure in conscious normotensive hypovolemic dogs was similar to that observed in renal hypotensive normovolemic dogs.

Heart rate changes accompanying the antihypertensive action of cilazapril in the rat and the dog were minimal.

Total peripheral resistance and regional vascular resistance were reduced in all vascular beds except in the heart in SHR administered multiple, oral, daily doses of 10 mg/kg cilazapril. Regional blood flow to the kidneys, intestine and skin increased. Regional blood flow to the heart decreased. No changes were observed in cardiac output, cardiac index, stroke volume or heart rate. Hemodynamic and blood flow changes were similar after acute or repeated (twice daily for two weeks) administration of 1 mg/kg cilazapril. Additional increases in blood flow to the lungs, stomach, small intestine, pancreas and thymus were observed, however.

In conscious dogs, cilazapril had no effect on left ventricular pressure and on force of cardiac contraction at 3 mg/kg p.o. and marginal effects at 10 mg/kg p.o. At these doses, slight decreases were noted in abdominal aortic blood flow and heart rate. In anesthetized dogs, intravenous cilazapril doses of 0.03-1 mg/kg evoked dose dependent decreases in blood pressure and left ventricular pressure. At 1 mg/kg, left ventricular end diastolic pressure was decreased 15%, myocardial contractile force was reduced and heart rate was unchanged. At 0.3 mg/kg, cardiac output, coronary blood flow, left ventricular minute work, left ventricular stroke work, and cardiac index were decreased 15%, 12%, 31%, 40%, and 12% respectively. In the anesthetized dog with ischemic heart failure, intravenous doses of cilazaprilat (0.1-1 mg/kg) reduced total peripheral resistance, left ventricular end diastolic pressure, dp/dt, and mean aortic blood pressure. Cardiac output, heart rate, pulmonary arterial pressure and right arterial pressure remained unchanged.

Oral administration of 3 mg/kg cilazapril did not have an effect on the increase in blood pressure and heart rate accompanying exercise in conscious cats. In anesthetized cats, cilazapril (10 mg/kg i.v.) increased right ventricular force of contraction (28%) and cardiac output (19%). Heart rate changes were minor.

The pharmacokinetics of cilazapril and cilazaprilat have been examined in mice, rats, dogs, monkeys, marmosets and baboons. The oral absorption of cilazapril is rapid and peak plasma concentrations of cilazapril occur in less than 1 hour. Absorption is 70-89%. Cilazapril plasma concentrations decline rapidly with a half-life of 0.7-2.7 hours. Plasma concentrations are less

than dose proportional in baboons, and in rats and marmoset levels are too low for reliable quantitation.

Cilazaprilat is produced rapidly in all species and peak concentrations occur in less than 1.5 hours. Bioavailability from oral cilazapril is 70-89%. Cilazaprilat plasma concentrations decline in a biphasic manner with half lives of 0.5-3.5 hours and 12-68 hours. Plasma concentrations are less than dose proportional, and show a low order of dose dependence during the terminal phase. This is consistent with saturable binding to ACE.

The distribution of drug related material is largely confined to excretory organs, but all major tissues are exposed, including the fetus of pregnant animals. There is no evidence of tissue retention, and more than 95% of the dose is recovered within three days. Repeat administration leads to some accumulation, but only in a limited number of tissues, notably the liver and kidney. Excretion is rapid in all species. More than 90% of the total recovery in urine is achieved within 24 hours. Excretion is predominantly hepatic in rats and baboons, and renal in marmosets.

Hydrochlorothiazide Pharmacology: Hydrochlorothiazide increases the renal excretion of sodium and chloride in approximately equivalent amounts with an accompanying volume of water and causes a simultaneous, usually minimal loss of bicarbonate. The excretion of ammonia is reduced slightly by hydrochlorothiazide and the blood ammonia concentration may be increased. The excretion of potassium is increased slightly. Calcium excretion is decreased by hydrochlorothiazide and magnesium excretion is increased.

Hydrochlorothiazide is eliminated rapidly by the kidney. Its rate of elimination is decreased somewhat by the co-administration of probenecid without, however, an accompanying reduction in diuresis.

For a complete discussion of the pharmacology of hydrochlorothiazide, please consult the Product Monographs for hydrochlorothiazide products.

Cilazapril/Hydrochlorothiazide Pharmacology: In view of the extensive preclinical and clinical experience available with cilazapril and hydrochlorothiazide individually, and also with hydrochlorothiazide in combination with other ACE inhibitors, only limited studies were undertaken to specifically examine the preclinical pharmacology of the combination.

Table 6
Pre-clinical Pharmacology Studies: Cilazapril/Hydrochlorothiazide

Study	Species	Route of Administration	Dose (mg/kg)	Results/ Observations
<p>Effects of HCTZ on cilazapril.</p> <p>Modulation by HCTZ of anti-hypertensive actions of cilazapril in spontaneously hypertensive rats.</p>	<p>Male SHR</p> <p>Unilaterally adrenal-demedullated and contralaterally adrenalectomized</p>	p.o.	<p>10 (cilazapril)</p> <p>30 (HCTZ)</p>	<p>Although HCTZ alone had no effect on blood pressure, it significantly increased (by up to 24 mm Hg) the reduction in blood pressure induced by cilazapril.</p>

TOXICOLOGY

Study	Species	Description	N	Dose/Route/Form	Conclusion
1	Rat	6-month oral toxicity	10 x 6M, 6F	0 (vehicle), 0.45 (0.2/0.25), 4.95 (2.2/2.75), 56.0 (24.9/31.1), 2.7 (0.2/2.5), 29.7 (2.2/27.5), 337.5 (25.0/312.5) cilazapril/ hydrochlorothiazide; 25.0 cilazapril alone; 31.0 and 312.5 hydrochlorothiazide alone/oral/suspension	No drug accumulation of CLZ ¹ or HCTZ ² after repetitive dosing of each alone. When CLZ/HCTZ was dosed, increasing HCTZ accumulation was observed with increasing HCTZ dose. HCTZ did not affect the disposition of CLZ when these drugs were co-administered.
2	Baboon	13-week toxicity	7 x 2M, 2F	0, 6.75 (0.5/6.25), 40.5 (3.0/37.5), 270 (20/250), 6.25 (0/6.25), 37.5 (0/37.5), 250 (0/250)/oral/suspension	Administration of CLZ/HCTZ in a 1:125 ratio at 40.5 or 270 mg/kg/d resulted in decreased plasma clearance of HCTZ and slight decrease of CLZ ³ plasma clearance by Day 7.
3	Baboon	26-week toxicity	4 x 2M, 2F	0, 1.125 (0.5/0.625), 6.75 (3.0/3.75), 45 (20/25)/oral/suspension	The disposition of CLZ and HCTZ remained largely unchanged during the 26 weeks of dosing.

¹ Cilazapril

² Hydrochlorothiazide

³ Cilazaprilat

Table 8 Cilazapril Acute Toxicity			
Species	Sex	Route	Approximate LD₅₀ (mg/kg)
Mouse	M	p.o.	4,600
	F	p.o.	2,500 - <5,000
	M + F	i.v.	>250
	M	i.p.	1,600
	F	i.p.	1,300
	M + F	s.c.	>1,000
Rat	M + F	p.o.	>4,000 - <5,000
	M + F	i.p.	830
Monkey	M + F	p.o.	>4,000 - <5,000

The signs of toxicity include: ataxia, reduced motor activity, diarrhea, respiratory depression, tremors, piloerection, prostration, hunched appearance, salivation, emesis and facial fur-staining.

Table 9 Cilazapril/Hydrochlorothiazide Acute Toxicity			
Species	Sex	Route	Observations/ LD₅₀ (mg/kg)
Mouse	M	p.o. ¹	CLZ ⁴ + HCTZ ⁵ (6:10) - 3,500 expressed as CLZ component. CLZ - 3,300 HCTZ - >8,300
Mouse Rat	M+F	p.o. ² p.o. ³	No mortalities or clinical observations were noted.

¹ *Gavage*

² *Capsule - 50 capsules/kg (mouse)*

³ *Capsule - 30 capsules/kg (rat)*

⁴ *Cilazapril*

⁵ *Hydrochlorothiazide*

Table 10
Long-Term Toxicity of Cilazapril

Species (#/group)	Study duration	Dose administration (mg/kg/day)	Route	Findings
Rat (8M + 8F)	2 Weeks	0, 2, 6, 20	i.v.	All dose groups: Swollen tails in individual rats after 8-10 days; slight increase in urine volume (males).
Monkey Marmoset (3M + 3F)	2 Weeks	0, 2, 6, 20	i.v.	All dose groups: Slightly depressed heart rates.
Rat (5M + 5F)	4 Weeks	0, 5, 15, 50	p.o.	All dose groups: Increased water consumption. 15 and 50 mg/kg/day: Minimal decreases in RBC, Hb and PCV values (females); increase in plasma urea (2-3x). 50 mg/kg/day: Salivation (6/10) from week 2; decrease body weight gain (20%); slight reduction in food consumption; increased incidence of kidney tubule cells in urine (females).

Table 10
Long-Term Toxicity of Cilazapril

Species (#/group)	Study duration	Dose administration (mg/kg/day)	Route	Findings
Rat (16M + 16F)	4 Weeks	25, 125, 625	p.o.	<p>All dose groups: Salivation; slight reduction in motor activity; increased urine volumes and minimal decreases in specific gravity (males).</p> <p>125 and 625 mg/kg/day: Decreased body weight gain and food consumption (males only at 125 mg/kg/day); slight decreases in RBC, Hb and PCV (males); very slight thickening of glomerular afferent arteriolar wall in the kidney (males) (1/10 - 125 mg/kg/day, 6/10 - 625 mg/kg/day).</p> <p>625 mg/kg/day: Increased BUN values (1.5x) (males); decreased BMC¹ (males); slight decrease in heart and liver (males) weight.</p>
Monkey Marmoset (3/6M + 3F)	4 Weeks	0, 5, 15, 50	p.o.	<p>15 and 50 mg/kg/day: Marginal decreases in RBC, Hb and PCV values.</p> <p>50 mg/kg/day: Increase in plasma urea (2x), K⁺ and cholesterol values; increased incidence of kidney tubule cells in urine.</p>

Table 10
Long-Term Toxicity of Cilazapril

Species (#/group)	Study duration	Dose administration (mg/kg/day)	Route	Findings
Rat (16M + 16F)	13 Weeks	0, 10, 50, 250	p.o.	<p>All dose groups: Very slight increases in urine volume and decreased SG values (males).</p> <p>50 and 250 mg/kg/day: Dose-related decrease in body weight gain (males only at 50 mg/kg/day); increased BUN levels (2x) (males); slight thickening of glomerular afferent arterioles in the kidneys (10/30).</p> <p>250 mg/kg/day: Slight decrease in spontaneous activity and salivation; inhibition of food consumption; small decreases in RBC and BMC (males), and in RBC, PCV and Hb (females).</p>
Monkey Cynomolgus (4M + 4F)	13 Weeks	0, 2.5, 25, 50	p.o.	<p>25 and 50 mg/kg/day: Slight decreases in RBC, Hb and PCV. Slight to moderate hyperplasia of the juxtaglomerular apparatus; dose-related decreased body weight gains.</p> <p>50 mg/kg/day: Two deaths; salivation; emesis; decreased spontaneous activity. Slight decrease in BMC, total protein and inorganic phosphate; increase in BUN (4x), blood creatinine; enlargement of kidney (1 female); reduction in heart weight; kidney tubular dilatation.</p>

Table 10
Long-Term Toxicity of Cilazapril

Species (#/group)	Study duration	Dose administration (mg/kg/day)	Route	Findings
Monkey Baboon (2M + 2F)	13 Weeks	0, 2, 10, 20, 40	p.o.	<p>All dose groups: Emesis; slight reductions in heart rate, body weight gain and heart weight; hypertrophy and hyperplasia of the juxtaglomerular cells (1/4 - 10 mg/kg, 3/4 - 20 mg/kg, 4/4 - 40 mg/kg).</p> <p>20 and 40 mg/kg/day: Slight decrease in RBC, PCV and Hb; kidney tubular basophilia/ dilatation (1/4 - 20 mg/kg; 3/4 - 40 mg/kg). Increased urea (2x) in 40 mg/kg only.</p>
Rat (30M + 30F)	26 Weeks	0, 5, 30, 200; 0, 2, 12, 75 - from Week 6; 0, 2, 12, 50 from Week 14	p.o.	<p>All dose groups: Slight decrease in heart rate; weight loss; lethargy; hunched posture. Piloerection; facial fur-staining; dose-related increases in kidney weights (male).</p> <p>12 and 50 mg/kg/day: Hypertrophy of afferent glomerular arterioles in the kidneys (13 weeks).</p> <p>50 mg/kg/day: Body weight gain decrease (14%) (males); increased water intake. Increased BUN levels (3x) (males), ALP activity, and liver weights (males); prominent kidney tubular regeneration; kidney tubular dilatation; minimal kidney tubular necrosis (2 animals at 13 weeks). Sclerosis (2 animals at 26 weeks).</p>

Table 10
Long-Term Toxicity of Cilazapril

Species (#/group)	Study duration	Dose administration (mg/kg/day)	Route	Findings
Monkey Marmoset (9, 7, 7, 11M+ 9, 7, 7, 11F)	26 Weeks	0, 5, 30, 200; 0, 2, 15, 100 from Week 9; 0, 2, 15, 50 from Week 14	p.o.	200 mg/kg/day: Depression in heart rate; body weight loss (females). 15 mg/kg/day: Two deaths (unrelated to treatment) of minor glomerular arteriolar hypertrophy (13 and 26 weeks). 50 mg/kg/day: Six deaths (two unrelated to treatment); unsteadiness; inactivity; salivation; emesis; diarrhea; slight decrease in RBC, PCV, Hb and bone marrow, myeloid/erythroid ratio (26 weeks). Increase in plasma urea (2x); small reductions in urine osmolality; slight kidney tubular dilatation and tubular epithelium regeneration (4/5 at 13 weeks - 100 mg/kg) (4/10 after 26 weeks).
Monkey Baboon (7M + 7F)	52 Weeks	0, 0.5, 4, 40	p.o.	4 and 40 mg/kg/day: Hyperplasia and hypertrophy of juxtaglomerular apparatus with hypertrophy of muscle cells of glomerular arterioles (1/10 - 4 mg/kg; 8/10 - 40 mg/kg/day). 40 mg/kg/day: Emesis; body weight gain reduction; slight reduction in RBC, PCV and Hb; increase in urea values (2x) and creatinine; osmolality reductions; increased incidence in proteinous casts (Week 52); small increase in adrenal and thyroid weights.

Table 10
Long-Term Toxicity of Cilazapril

Species (#/group)	Study duration	Dose administration (mg/kg/day)	Route	Findings
Rat (35M + 35F)	78 Weeks	0, 0.5, 4, 40	p.o.	<p>All dose levels: Small reductions in body weight gain.</p> <p>4 and 40 mg/kg/day: Slight decrease in RBC, PCV and Hb; minimal reduction in food intake; increase in BUN (2x) (males).</p> <p>40 mg/kg/day: Increased water consumption; slight increase in total WBC count (males); increased urine volumes (males); irregular surface ocysts in the kidneys (7/40 at 76 weeks); increased kidney weights (males); slight decrease in heart and liver weight (females); vascular hypertrophy (20/20 males, 17/20 females) consisting of glomerular afferent arteriolar wall thickening; similar but less frequent and less severe changes were observed in the mid-dose group.</p>

¹ Bone marrow nucleated cell count

Hydrochlorothiazide Toxicology: For a complete discussion of the Toxicology of hydrochlorothiazide, please consult the Product Monograph for HYDRODIURIL (Merck Sharp & Dohme Canada).

Hydrochlorothiazide was found to have relatively low toxicity in acute and chronic toxicity studies. In acute animal toxicity studies in mice the LD₅₀ was greater than 10,000 mg/kg suspension orally and was 884 mg/kg intravenously. In rats the acute LD₅₀ was greater than 10,000 mg/kg suspension orally and 3,130 mg/kg suspension intraperitoneally. In the rabbit the acute intravenous LD₅₀ was 461 mg/kg and in the dog it was approximately 1,000 mg/kg. Dogs tolerated at least 2,000 mg/kg orally without signs of toxicity.

Subacute oral toxicity studies in the rat at 500, 1,000 and 2,000 mg/kg/day of suspension five days a week for three weeks displayed no sign of drug effect. Three of the rats given 2,000 mg/kg/day hydrochlorothiazide sodium salt died after the fifth day. These deaths were attributed to pneumonia. No sign of drug effect was observed among the other animals. In dogs given doses of 250, 500 and 1,000 mg/kg seven days a week for 8 weeks, no gross signs of drug effect were noted except for electrolyte imbalance.

Chronic oral toxicity studies in the rat using doses of up to 2,000 mg/kg/day 5 days per week for 26 weeks showed no signs of drug effect and no drug related changes on post-mortem examination. In dogs, oral doses of 0, 125, 250 mg/kg/day 5 days per week for 26 weeks; 500 mg/kg/day for 7 weeks; 11 weeks without drug then 500 mg/kg/day 7 days per week for 8 weeks, were given. Slight depression of plasma potassium, small amounts of yellow crystalline precipitate in the bladder in two of twelve dogs were found on gross examination. Histomorphologic studies did not show drug related changes.

Hydrochlorothiazide has been administered to rats in a two-litter study, to mice in a two-generation study, and to rabbits in an established pregnancy test. None of these studies showed any evidence of teratogenic effects of hydrochlorothiazide. Offspring carried on to weaning or maturity did not show evidence of effects related to treatment.

Table 11
Long-Term Toxicity (Cilazapril / Hydrochlorothiazide)

Species (No./Group)	Study Duration	Doses (mg/kg/day)/Route of Administration	Effects
			sodium and serum chloride; decrease serum triglycerides and serum calcium (M); increase kidney weight and decrease absolute heart weight (M); relative thyroid weight increase (F); hypertrophy and hyperplasia of the juxtaglomerular apparatus and hypertrophy of the renal afferent arterioles.
		c) CLZ - 25 d) HCTZ - 31; 312.5	c) CLZ - 25 - 38% increase in serum BUN (M) and decrease in serum sodium; hypertrophy and hyperplasia of the juxtaglomerular arterioles and hypertrophy of the renal afferent arterioles. d) HCTZ - 31 - decrease in serum sodium (F), serum chloride and serum potassium. 312.5 - decrease in serum sodium (F), serum potassium and serum chloride, increase in absolute and relative kidney and thyroid weights (F).
Baboon 6M + 6F)	26 Weeks (8-Week recovery for 2/sex/group)	0 (vehicle control) CLZ + HCTZ (1:1.25): 0.5 + 0.625; 3 + 3.75; 20 + 25 P.O. (gavage)	CLZ + HCTZ (1:1.25) <u>3</u> + - reversible decrease in body weight gain (M), decrease <u>3.75</u> in urine specific gravity. - low grade hypertrophy of juxtaglomerular cells of kidneys. <u>20</u> + - decrease in body weight gain and motor activity; <u>25</u> - reversible reduction in erythrocyte levels and reversible increase in serum BUN, serum creatinine and serum

Table 11
Long-Term Toxicity (Cilazapril / Hydrochlorothiazide)

Species (No./Group)	Study Duration	Doses (mg/kg/day)/Route of Administration	Effects
			calcium; - decrease in urine specific gravity and serum phosphorus; - hypertrophy of renal afferent glomerular arterioles and juxtaglomerular cells.

¹ Male

² Female

³ Cilazapril

⁴ Hydrochlorothiazide

Cilazapril Carcinogenicity: An 88-week carcinogenicity study with cilazapril was conducted in mice initially dosed at 5, 25 or 100 mg/kg/day, subsequently reduced to 1, 7 or 50 mg/kg/day from week 11 onwards. Another carcinogenicity study was conducted in rats in which dose levels of 0.5, 4 or 40 mg/kg/day were administered for 104 weeks. Hypertrophy of renal afferent glomerular arterioles and interlobular arteries, and increased cortical nephropathy were the only recorded findings and occurred in the mid- and high-dose groups in both studies.

Hydrochlorothiazide Carcinogenicity: According to the experimental data available, hydrochlorothiazide revealed inconsistent evidence of carcinogenic activity in rats and mice, with conflicting evidence of hepatic adenoma in male mice at the highest dose and adrenal pheochromocytoma in one rat study but not in another. Current evidence is inadequate to draw a clear conclusion for a carcinogenic effect of hydrochlorothiazide in animals.

The mutagenic potential was assessed in a series of *in vitro* and *in vivo* test systems. While some positive results were obtained *in vitro*, all *in vivo* studies provided negative results. Hydrochlorothiazide enhanced the UVA-induced formation of pyrimidine dimers *in vitro* and in the skin of mice following oral treatment. It is therefore concluded that although there is no relevant mutagenic potential *in vivo*, hydrochlorothiazide could enhance the genotoxic effects of UVA light. This mechanism of photosensitization could be associated with a higher risk for non-melanoma skin cancer.

Cilazapril Mutagenicity: No evidence of mutagenicity with cilazapril was found in the Ames test with or without metabolic activation (up to 2.0 mg/plate), Treatment and Plate test (up to 7,000 µg/mL), unscheduled DNA synthesis assay (up to 200 µg/mL), mutagenic assay with Chinese hamster V79 cells with or without metabolic activation (up to 4,800 µg/mL), chromosomal aberration test with or without metabolic activation (up to 3,500 µg/mL), or *in vivo* micronucleus test in mice (2.0 g/kg).

Cilazapril/Hydrochlorothiazide Mutagenicity: The Ames tests showed evidence of weak mutagenicity for cilazapril in combination with hydrochlorothiazide with and without metabolic activation. The activity was considered borderline but was reproducible and dose-dependent. This mutagenic effect correlated with the weak mutagenicity of the hydrochlorothiazide component of the combination.

The mutagenicity of the combination cilazapril and hydrochlorothiazide (at a ratio of 1:5) was assessed in the three additional mutagenicity tests. There was no evidence of gene mutation either in the presence or absence of exogenous metabolizing systems when the combination was tested in *saccharomyces cerevisiae* D7 yeast strain (up to 5,000 µg/mL) and in Chinese hamster V79 cells (up to 1,920 µg/mL). In addition, a mouse micronucleus tests (*in vivo*) carried out with a 1:5 combination of cilazapril and hydrochlorothiazide (up to 4.0 g/kg) showed no genotoxic activity in mouse bone marrow cells.

Table 12
Reproduction and Teratology (Cilazapril)

Species #/Group	Dose (mg/kg/day)	Route	Duration Of Dosing	Effects
Fertility and General Reproduction Performance				
Rat Charles River (CrI:CD (SD) BR) (30M + 30F)	0, 1, 7, 50	p.o.	Males - 70 days prior to mating and up to 14 days during mating. Females - 14 days before mating, during gestation and until Day 21 post-partum.	All dose groups: No effect on mating or fertility at any dose. Retching reflex after dosing (dose-related) (males). Decreased body weight gain. Males at 50 mg/kg/day: Six deaths (due to dosing error). Females at 50 mg/kg/day: Two deaths (50 mg/kg) (due to dosing error). Increased preimplantation loss (forced delivery group at 50 mg/kg). F ₁ generation at 7 and 50 mg/kg/day: Reduced body weight at the end of lactation; increased incidence of dilatation of the renal pelvis. Reduction in viable fetuses due to a lower number of implantations (50 mg/kg).
Embryotoxicity				
Rat Charles River (CD) (35F)	0, 2, 30, 400	p.o.	Days 6-17 of gestation.	All dose groups: No effect on embryonic, fetal or postnatal development. Females at 400 mg/kg/day: Body weight gain and food consumption were reduced during latter half of gestation. F ₁ generation at 400 mg/kg/day: Slight increase in renal cavitation incidence.

Table 12
Reproduction and Teratology (Cilazapril)

Species #/Group	Dose (mg/kg/day)	Route	Duration Of Dosing	Effects
Fertility and General Reproduction Performance				
Monkey Cynomolgus (10 or 11F)	0, 20	p.o.	Days 21 to 31 or Days 32 to 45 of gestation.	Control group: Reduced food consumption and diarrhea (5/10 females); 2/10 abortions between Days 51-53 of pregnancy; low incidence of skeletal variations in tail (2/8 fetuses) and ribs (2/8). 20 mg/kg/day - Days 21-31: Reduced food consumption (10/10 females); diarrhea (2/10); vomiting (2/10). Skeletal findings - ribs (2/8 fetuses), humeri (2/8), distal caudal variations (4/8), and prepuce not patent (2/8) - not treatment related. 20 mg/kg/day - Days 32-45: Decreased food consumption and/or diarrhea (11/11 females); 5/11 abortions; 2/11 maternal deaths (not treatment related). Caudal and humerus variations (1/5 fetuses) - not treatment related.
Peri- and Post-natal Toxicity				
Rat Charles River (CD1:CD(SD) BR) (25 or 30F)	0, 1, 7, 50	p.o.	Day 15 of gestation to Day 21 post-partum.	Females at 50 mg/kg/day: 5 deaths on Day 18 postcoitus or Days 4-16 of lactation (due to dosing error). F ₁ generation at 50 mg/kg/day: Increased pup mortality (4.9%); reduction in body weight gain during lactation; an associated slight delay in pinna unfolding.

Table 13
Reproduction and Teratology (Cilazapril / Hydrochlorothiazide)

Species (No./Sex/Dose)	Treatment Days (Day Of Sacrifice)	Doses (mg/kg/day)/ Route Of Administration	Effects	
Mouse (6F) Segment II	Gestation days: 6-17 (18)	0 (vehicle control) CLZ + HCTZ (1:5): + 31; 25 + 125; 100 + 500; 400 + 2,000 P.O. (gavage)	<u>100 +</u> <u>500:</u>	- decrease in maternal body weight and slight increase post-implantation loss and resorption rate.
			<u>400 +</u> <u>2,000:</u>	- decrease in maternal body weight and food consumption and an increase in salivation; - decrease in fetal body weight and slight increase in post-implantation loss
Mouse (25F) Segment II	Gestation days: 6-15 (18)	0 (vehicle control) CLZ + HCTZ (1:5): 6 + 30; 50 + 250; 400 + 2,000 P.O. (gavage)	<u>50 +</u> <u>250:</u>	- reduced ossification of frontal bones.
			<u>400 +</u> <u>2,000:</u>	- slight decrease in maternal body weight gain starting day 6 of gestation; increase incidence of dilated renal pelvises, reduced ossification of frontal and parietal bones, misaligned sternbrae and sternbrae variants.
		0 (vehicle control) CLZ + HCTZ (1:5): 6 + 31; 40 + 200; 90 + 450; 200 + 1,000 P.O. (gavage)	<u>6 + 31:</u>	- muzzle staining.
			<u>40 +</u> <u>200:</u>	- muzzle staining, salivation and decrease in maternal body weight gain and food consumption. - decrease gravid uterine weights and fetal weights.
			<u>90 +</u> <u>450:</u>	- muzzle staining, salivation and decrease in maternal body weight gain and food consumption. - decrease gravid uterine weights and fetal weights.

Table 13
Reproduction and Teratology (Cilazapril / Hydrochlorothiazide)

Species (No./Sex/Dose)	Treatment Days (Day Of Sacrifice)	Doses (mg/kg/day)/ Route Of Administration	Effects	
				<ul style="list-style-type: none"> - one dam found dead on gestation Day 20 exhibited tremors, hunched posture, weakness, uncoordinated and decreased movement and decreased respiration on gestation Day 19; a relationship to treatment cannot be excluded.
Rat (6F) Segment II	Gestation days: 7-17 (20)		<u>200 +</u> <u>1,000:</u>	<ul style="list-style-type: none"> - muzzle staining, salivation, decrease in maternal body weight gain and food consumption. - decrease gravid uterine weights and fetal weights. - one dam was scarificed on gestation Day 19 after delivering three fetuses. This dam had red stained fur, decreased motor activity, decreased temperature, hunched position, labored respiration, weakness, thin condition and signs of dehydration; a relationship to treatment cannot be excluded.
Rat (25F) Segment II	Gestation days: 7-17 (20)	0 (vehicle control) CLZ + HCTZ (1:5): 6 + 31; 16 + 80; 40 + 200; P.O. (gavage)	<u>>6 +</u> <u>31:</u> <u>>16 +</u> <u>80:</u> <u>40 +</u> <u>200:</u>	<ul style="list-style-type: none"> - decrease maternal body weight gain and food consumption. - decrease in fetal weights - increase in minor skeletal anomalies (retarded ossification in a variety of bones). Considered to be secondary to decreased fetal weights.

PART III: CONSUMER INFORMATION

PrINHIBACE PLUS®
cilazapril and hydrochlorothiazide
tablets

Read this carefully before you start taking INHIBACE PLUS and each time you get a refill. This leaflet is a summary and will not tell you everything about INHIBACE PLUS. Talk to your doctor, nurse, or pharmacist about your medical condition and treatment and ask if there is any new information about INHIBACE PLUS.

ABOUT THIS MEDICATION

What the medication is used for:

INHIBACE PLUS lowers high blood pressure.

What it does:

INHIBACE PLUS contains a combination of 2 drugs: cilazapril and hydrochlorothiazide.

- Cilazapril is an angiotensin-converting enzyme (ACE) inhibitor. You can recognize ACE inhibitors because their medicinal ingredient ends in ‘-PRIL’. It lowers blood pressure.
- Hydrochlorothiazide is a diuretic or “water pill” that increases urination. This lowers blood pressure.

This medicine does not cure high blood pressure. It helps to control it. Therefore, it is important to continue taking INHIBACE PLUS regularly even if you feel fine.

When it should not be used:

Do not take INHIBACE PLUS if you:

- Are allergic to cilazapril or hydrochlorothiazide or to any non-medicinal ingredient in the formulation.
- Are allergic to any other blood pressure medicines of the same class (called ACE inhibitors).
- Are allergic to any sulfonamide-derived drugs (sulfa drugs); most of them have a medicinal ingredient that ends in “-MIDE”.
- Have experienced an allergic reaction (angioedema) with swelling of the hands, feet, or ankles, face, lips, tongue, throat, or sudden difficulty breathing or swallowing, to any ACE inhibitor or without a known cause. Be sure to tell your doctor, nurse, or pharmacist that this has happened to you.
- Have been diagnosed with hereditary angioedema: an increased risk of getting an allergic reaction that is passed down through families. This can be triggered by different factors, such as surgery, flu, or dental procedures.
- Have difficulty urinating or produce no urine.

- Have a build up of fluid in your abdomen (ascites).
- Are taking a medicine containing a neprilysin inhibitor (e.g., sacubitril/valsartan), as the risk of angioedema is increased. Do not take INHIBACE PLUS for at least 36 hours before or after you take sacubitril/valsartan, a medicine used to treat heart failure.
- Are pregnant or intend to become pregnant. Taking INHIBACE PLUS during pregnancy can cause injury and even death to your baby.
- Are breastfeeding. INHIBACE PLUS passes into breast milk.
- Are lactose intolerant or have one of the following rare hereditary diseases:
 - Galactose intolerance
 - Lapp lactase deficiency
 - Glucose-galactose malabsorption
 because lactose is a non-medicinal ingredient in INHIBACE PLUS.
- Are already taking a blood pressure-lowering medicine that contains aliskiren (such as RASILEZ) and you have diabetes or kidney disease.

What the medicinal ingredients are:

cilazapril and hydrochlorothiazide

What the non-medicinal ingredients are:

cornstarch, hydroxypropyl methylcellulose, lactose, red iron oxide, sodium stearyl fumarate, talc, and titanium dioxide.

What dosage forms it comes in:

Tablets; 5 mg cilazapril and 12.5 mg hydrochlorothiazide

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions - Pregnancy

INHIBACE PLUS should not be used during pregnancy. If you discover that you are pregnant while taking INHIBACE PLUS, stop the medication and contact your doctor, nurse, or pharmacist as soon as possible.

BEFORE you use INHIBACE PLUS talk to your doctor, nurse or pharmacist if you:

- Are allergic to any drug used to lower blood pressure.
- Are allergic to penicillin.
- Have recently received or are planning to get allergy shots for bee or wasp stings.
- Have narrowing of an artery or a heart valve.
- Have had a heart attack or stroke.
- Have heart failure.
- Have diabetes, liver or kidney disease.
- Are on dialysis.
- Have lupus or gout.
- Have had skin cancer or have a family history of skin cancer.

- Have a greater chance of developing skin cancer because you have light-coloured skin, get sunburned easily, or are taking drugs to suppress your immune system.
- Have a collagen disease (skin disease) such as lupus (systemic lupus erythematosus) or scleroderma (a skin condition leading to hardening or thickening of the skin).
- Are on LDL apheresis (a treatment to lower the LDL cholesterol in the blood).
- Are dehydrated or recently suffered from excessive vomiting, diarrhea, or sweating.
- Are taking a salt substitute that contains potassium, potassium supplements, or a potassium-sparing diuretic (a specific kind of “water pill”) or other drugs that may increase serum potassium (e.g. trimethoprim-containing products).
- Are on a low-salt diet.
- Are receiving gold (sodium aurothiomalate) injections.
- Are less than 18 years old. INHIBACE PLUS is not recommended for use in children.
- Are taking a medicine that contains aliskiren, such as RASILEZ, used to lower high blood pressure. The combination with INHIBACE PLUS is not recommended.
- Are taking any of the following medicines, the risk of angioedema may be increased:
 - Medicines used to prevent organ transplant rejection and for cancer (e.g. temsirolimus, sirolimus, everolimus).
 - DPP-IV inhibitors (e.g. alogliptin, linagliptin, saxagliptin and sitagliptin, medicines used to treat diabetes).
- Are taking an angiotensin receptor blocker (ARB). You can recognize an ARB because its medicinal ingredient ends in “-SARTAN”.

Risk of skin cancer:

INHIBACE PLUS contains hydrochlorothiazide. Treatment with hydrochlorothiazide may increase the risk of developing non-melanoma skin cancer. The risk is higher if you have been taking INHIBACE PLUS for many years (more than 3) or at a high dose.

While taking INHIBACE PLUS:

- Make sure to regularly check your skin for any new lesions. Check areas that are most exposed to the sun, such as the face, ears, hands, shoulders, upper chest and back.
- Limit your exposure to the sun and to indoor tanning. Always use sunscreen (SPF-30 or higher) and wear protective clothing when going outside.
- Talk to your doctor immediately if you get more sensitive to the sun or UV light or if you develop an unexpected skin lesion (such as a lump, bump, sore, or patch) during the treatment.

Hydrochlorothiazide in INHIBACE PLUS can cause Sudden Eye Disorders:

- **Myopia:** sudden nearsightedness or blurred vision.
- **Glaucoma:** an increased pressure in your eyes, eye pain. Untreated, it may lead to permanent vision loss.

These eye disorders are related and can develop within hours to weeks of starting INHIBACE PLUS.

You may become sensitive to the sun while taking INHIBACE PLUS. Exposure to sunlight should be minimized until you know how you respond.

If you are going to have surgery and will be given an anesthetic, be sure to tell your doctor or dentist that you are taking INHIBACE PLUS.

Driving and using machines: Before you perform tasks, which may require special attention, wait until you know how you respond to INHIBACE PLUS. Dizziness, lightheadedness, or fainting can especially occur after the first dose and when the dose is increased.

INTERACTIONS WITH THIS MEDICATION

As with most medicines, interactions with other drugs are possible. Tell your doctor, nurse, or pharmacist about all the medicines you take, including drugs prescribed by other doctors, vitamins, minerals, natural supplements, or alternative medicines.

The following may interact with INHIBACE PLUS:

- Adrenocorticotrophic hormone (ACTH) used to treat West Syndrome.
- Agents increasing serum potassium, such as a salt substitute that contains potassium, potassium supplements, potassium-sparing diuretics (a specific kind of “water pill,” e.g. spironolactone, triamterene, amiloride and eplerenone) or other drugs that may increase serum potassium (e.g. trimethoprim-containing products and co-trimoxazole for infections caused by bacteria; cyclosporine, an immunosuppressant medicine used to prevent organ transplant rejection; and heparin, a medicine used to thin blood to prevent clots).
- Alcohol, barbiturates (sleeping pills), or narcotics (strong pain medications). They may cause low blood pressure and dizziness when you go from lying or sitting to standing up.
- Amphotericin B, an antifungal drug.
- Anticancer drugs, including cyclophosphamide and methotrexate.
- Antidepressants, in particular selective serotonin reuptake inhibitors (SSRIs), including citalopram, escitalopram, sertraline, and tricyclic antidepressants (e.g. amitriptyline, clomipramine, imipramine).

- Antipsychotics.
- Antidiabetic drugs, including insulin and oral medicines.
- Bile acid resins used to lower cholesterol.
- Calcium or vitamin D supplements.
- Corticosteroids used to treat joint pain and swelling.
- Digoxin, a heart medication.
- Drugs that slow down or speed up bowel function, including atropine, metoclopramide, and domperidone.
- Drugs used to treat epilepsy, including carbamazepine and topiramate.
- Drugs used to treat irregular heartbeat
- Gout medications, including allopurinol and probenecid.
- Lithium used to treat bipolar disease.
- Nonsteroidal anti-inflammatory drugs (NSAIDs), used to reduce pain and swelling. Examples include ibuprofen, naproxen, and celecoxib.
- Other blood pressure lowering drugs. When taken in combination with INHIBACE PLUS, they may cause excessively low blood pressure.
- Skeletal muscle relaxants used to relieve muscle spasms, including tubocurarine.
- Gold salts for the treatment of rheumatoid arthritis.
- Tetracycline, an antibiotic
- Amantadine, an antiviral
- Iodine containing contrast media
- Blood pressure-lowering drugs, including diuretics (“water pills”), aliskiren-containing products (e.g. RASILEZ), or angiotensin receptor blockers (ARBs).
- mTOR inhibitors (e.g. temsirolimus, sirolimus, everolimus)
- DPP-IV inhibitors (e.g. alogliptin, linagliptin, saxagliptin and sitagliptin)

PROPER USE OF THIS MEDICATION

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

Take INHIBACE PLUS exactly as prescribed. It is recommended to take your dose at about the same time every day.

INHIBACE PLUS tablets must not be chewed or crushed and should always be taken with a full glass of water.

INHIBACE PLUS can be taken with or without food. If INHIBACE PLUS causes upset stomach, take it with food or milk.

Overdose:

If you think you have taken too much INHIBACE PLUS contact your doctor, nurse, pharmacist, hospital emergency department or regional Poison control Centre immediately, even if there are no symptoms.

Missed Dose:

If you have forgotten to take your dose during the day, carry on with the next one at the usual time. Do not double dose.

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

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Side effects may include:

- Dizziness, headache, trouble sleeping
- Drowsiness, feeling tired, weakness
- Dry cough, dry or swollen mouth
- Runny or blocked nose, sneezing
- Rash, itching
- Abdominal pain, upset stomach, decreased appetite
- Diarrhea, constipation, nausea, vomiting
- Change in the way things taste
- Muscle cramps and/or joint pain, pins and needles sensation
- Sweating more than usual, flushing

If any of these affects you severely, tell your doctor, nurse or pharmacist.

INHIBACE PLUS can cause abnormal blood test results. Your doctor will decide when to perform blood tests and will interpret the results.

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

Symptom / effect		Talk to your healthcare professional		Stop taking drug and get immediate medical help
		Only if severe	In all cases	
Common	Low Blood Pressure: Dizziness, fainting, lightheadedness May occur when you go from lying or sitting to standing up.	✓		
	Non-melanoma skin cancer: Lump or discoloured patch on the skin that stays after a few weeks and slowly changes. Cancerous lumps are red/pink and firm and sometimes turn into ulcers. Cancerous patches are usually flat and scaly.		✓	
	Decreased or increased levels of potassium in the blood: Irregular heartbeats, muscle weakness and generally feeling unwell.		✓	

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

Symptom / effect		Talk to your healthcare professional		Stop taking drug and get immediate medical help
		Only if severe	In all cases	
Uncommon	Angioedema and Severe Allergic Reaction (anaphylaxis): Swelling of the face, eyes, lips, tongue or throat, difficulty swallowing or breathing, wheezing, rash, hives, itching, fever, abdominal cramps, chest discomfort or tightness.			✓
	Heart Attack: Chest pain and pressure (can be radiating from the left arm), heart palpitations, nausea, vomiting, trouble breathing, sweating, anxiety.			✓

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

Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Kidney Disorder: Change in frequency of urination, nausea, vomiting, swelling of extremities, fatigue.		✓	
Liver Disorder: Yellowing of the skin or eyes, dark urine, abdominal pain, nausea, vomiting, loss of appetite.		✓	
Increased blood sugar: Frequent urination, thirst, and hunger.	✓		
Electrolyte Imbalance: Weakness, drowsiness, muscle pain or cramps, irregular heartbeat.		✓	
Fast or irregular heartbeat		✓	
Chest pain (Angina)		✓	
Lupus-Like Syndrome: Fever, fatigue, joint and muscle pain, generally feeling unwell.		✓	

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

Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Breathing problems, including shortness of breath, trouble breathing, tightness in the chest, cough, wheezing.			✓
Rare			
Decreased Platelets: Bruising, bleeding, fatigue and weakness.		✓	
Decreased White Blood Cells: Infections (e.g. sore throat, fever), fatigue, aches, pains, and flu-like symptoms.		✓	

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

Symptom / effect		Talk to your healthcare professional		Stop taking drug and get immediate medical help
		Only if severe	In all cases	
Very rare	Serious skin reactions (Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis): Any combination of itchy skin rash, redness, blistering and severe peeling of the skin and/or inside of the lips, eyes, mouth, nasal passages or genitals, accompanied by fever, chills, headache, cough, body aches or swollen glands, joint pain, yellowing of the skin or eyes, dark urine.			✓
Unknown	Eye disorders: - Myopia: Sudden near sightedness or blurred vision. - Glaucoma: Increased pressure in your eyes, eye pain.			✓

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

Symptom / effect		Talk to your healthcare professional		Stop taking drug and get immediate medical help
		Only if severe	In all cases	
	Stroke: Weakness, blurred vision, trouble speaking, slurred speech, face drooping, dizziness, headache.			✓
	Anemia: Fatigue, loss of energy, weakness, shortness of breath.		✓	
	Inflammation of the Pancreas: Abdominal pain that lasts and gets worse when you lie down, nausea, vomiting.		✓	

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

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (<http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

HOW TO STORE IT

Store between 15-30°C.

Keep container tightly closed.

Keep out of reach and sight of children.

Return all unused or expired tablets to your doctor, nurse or pharmacist for safe disposal. Do not throw them away with your household waste.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:

[Health Canada website \(https://health-products.canada.ca/dpd-bdpp/index-eng.jsp\)](https://health-products.canada.ca/dpd-bdpp/index-eng.jsp) or by calling 1-888-XEDITON (933-4866).

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