PRODUCT MONOGRAPH

[Pr]CILAZAPRIL

(cilazapril monohydrate tablets)

1 mg, 2.5 mg and 5 mg

Angiotensin Converting Enzyme Inhibitor

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(cilazapril monohydrate tablets)

1 mg, 2.5 mg and 5 mg

THERAPEUTIC CLASSIFICATION

Angiotensin Converting Enzyme Inhibitor

ACTIONS AND CLINICAL PHARMACOLOGY

CILAZAPRIL (cilazapril) is an angiotensin converting enzyme (ACE) inhibitor, which is used in the treatment of hypertension and congestive heart failure.

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 hydrolysed 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.

Hypertension

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 effect of cilazapril in hypertensive patients and in patients with congestive heart failure 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 antihypertensive effect of angiotensin converting enzyme inhibitors, including cilazapril is generally lower in black patients 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.

Congestive Heart Failure

In patients with congestive heart failure the renin-angiotensin-aldosterone and the sympathetic nervous systems are generally activated leading to enhanced systemic vasoconstriction and to the promotion of sodium and water retention. By suppressing the renin-angiotensin-aldosterone system, cilazapril improves loading conditions in the failing heart by reducing systemic vascular resistance (afterload) and pulmonary capillary wedge pressure (preload) in patients on diuretics and/or digitalis. The onset of action of cilazapril occurs within 1-2 hours, reaching its maximum effect within 2-4 hours after the first dose. The exercise tolerance of these patients was increased and was associated with an improvement of clinical symptomatology. Patients studied belonged primarily to New York Heart Association Class II and III. The effect of cilazapril on survival in patients with heart failure has not been evaluated.

Pharmacokinetics

Cilazapril is well absorbed and rapidly converted 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:

Oral	**Cilazapril**		**Cilazaprilat**	
Dose (mg)	**C_{max} (ng/mL)**	**t_{max} (h)**	**C_{max} (ng/mL)**	**t_{max} (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% after1 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.

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.

Pharmacokinetics in Special Populations

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.

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.

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.

In patients with congestive heart failure the clearance of cilazaprilat is correlated with the creatinine clearance. Thus, dosage adjustments beyond those recommended for patients with impaired renal functions (see DOSAGE AND ADMINISTRATION under Congestive Heart Failure) should not be necessary.

Comparative Bioavailabilty

A comparative, two-way, single-dose crossover bioavailability study was performed on two cilazapril tablets, CILAZAPRIL 5 mg film-coated tablets and Inhibace® 5 mg tablets, under fasting conditions.

TABLE OF COMPARATIVE BIOAVAILABILITY DATA
CILAZAPRIL FILM-COATED TABLETS
(1 x 5 mg)

Cilazapril
From measured data
Geometric Mean
Arithmetic Mean (CV%)

Parameters	CILAZAPRIL	Inhibace®**	Ratio of Geometric Means (%)	90% Confidence Interval
AUC_{o-t} (ng •h/mL)	221.03 233.67 (36.51)	218.33 235.18 (44.20)	101.2	96.9-105.8
AUC_I (ng •h/mL)	221.99 234.61 (36.45)	219.30 236.11 (44.10)	101.2	96.9-105.7
C_{max} (ng/mL)	123.99 129.26 (28.78)	118.84 126.97 (39.43)	104.3	95.8-113.6
T_{max}* (h)	0.76 (45.53)	1.04 (40.49)	-	-
$T_{1/2}$* (h)	1.47 (31.62)	1.55 (45.63)	-	-

*T_{max} and $T_{1/2}$ are expressed as arithmetic mean (CV%) only.
**Inhibace® 5 mg Tablets (Hoffmann-La Roche Limited, Canada); purchased in Canada.

INDICATIONS AND CLINICAL USE

CILAZAPRIL (cilazapril) is indicated in the treatment of mild to moderate essential hypertension. CILAZAPRIL may be used alone or in combination with thiazide-type diuretics. CILAZAPRIL is also indicated in the treatment of congestive heart failure as an adjunctive therapy with digitalis and/or diuretics.

In using CILAZAPRIL consideration should be given to the risk of angioedema (see WARNINGS).

Hypertension

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

CILAZAPRIL can also be tried as an initial agent in those patients in whom use of diuretics and/or beta-blockers is contraindicated or in patients with medical conditions in which these drugs frequently cause serious adverse effects.

The safety and efficacy of cilazapril in renovascular hypertension has not been established and therefore, its use in this condition is not recommended.

The safety and efficacy of concomitant use of cilazapril with antihypertensive agents other than thiazide diuretics has not been established.

Congestive Heart Failure

CILAZAPRIL is indicated in the treatment of congestive heart failure as adjunctive therapy in patients who have not responded adequately to digitalis and/or diuretics. There is limited data on New York Heart Association Class IV patients (see ACTIONS AND CLINICAL PHARMACOLOGY). Treatment with CILAZAPRIL should be initiated in patients with congestive heart failure under close medical supervision.

CONTRAINDICATIONS

CILAZAPRIL (cilazapril) is contraindicated in patients who are hypersensitive to cilazapril, its components or other ACE inhibitors. CILAZAPRIL is also contraindicated in patients with a history of angioedema related to previous treatment with an angiotensin converting enzyme inhibitor and in patients with ascites.

WARNINGS

Serious Warnings and Precautions

When used in pregnancy, angiotensin converting enzyme (ACE) inhibitors can cause injury or even death of the developing fetus. When pregnancy is detected, CILAZAPRIL (cilazapril) should be discontinued as soon as possible.

Angioedema

Angioedema has been reported in patients treated with cilazapril. Angioedema associated with laryngeal edema and/or shock may be fatal. If angioedema occurs, CILAZAPRIL should be promptly discontinued and appropriate therapy instituted without delay. The patient should be followed carefully until the swelling has resolved. Swelling confined to the face, lips and mouth usually resolves without treatment, although antihistamines may provide symptomatic relief. Swelling of the tongue, glottis or larynx, may cause airway obstruction, therefore, subcutaneous adrenaline (0.5 mL 1:1000) should be administered promptly when indicated.

The incidence of angioedema during ACE inhibitor therapy has been reported to be higher in black than in non-black patients.

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).

Hypotension

Occasionally, symptomatic hypotension has occurred after administration of cilazapril usually after the first dose or when the dose had been increased. It is more likely to occur in patients with sodium or volume depletion in connection with diuretic therapy, dietary salt restriction, dialysis, diarrhea, or vomiting. Patients with congestive heart failure, especially those vigorously treated with loop diuretics, may experience excessive hypotension in response to ACE inhibitors. Because of the potential fall in blood pressure in these patients, therapy should be started under very close medical supervision. Such patients should be followed closely for the first two weeks of treatment and whenever the dose of CILAZAPRIL and/or diuretic is increased. Similar considerations may apply to patients with ischemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident (see ADVERSE REACTIONS).

In patients with severe heart failure, whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors, including cilazapril, may be associated with oliguria and/or progressive azotemia and rarely acute renal failure and/or death.

If hypotension occurs, the patient should be placed in supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response does not necessitate discontinuation of CILAZAPRIL. Once the blood pressure has increased after volume

expansion, CILAZAPRIL therapy may be continued. If symptoms persist, the dosage should be reduced or the drug discontinued.

Two elderly male patients, with a history of previous myocardial infarctions, on high diuretic dosage (240 mg and 120 mg of furosemide daily, respectively) for congestive heart failure NYHA Class III died within 8 hours after the addition of a single dose of 2.5 mg of cilazapril.

Neutropenia/Agranulocytosis

Agranulocytosis and bone marrow depression have been caused by ACE inhibitors. Cases of leucopenia and neutropenia have rarely been reported in patients treated with cilazapril. However, in no patient could a causal relationship to cilazapril be established. Periodic monitoring of white blood cell counts should be considered, especially in patients with collagen vascular disease and renal disease.

Pregnant Women

ACE inhibitors can cause fetal and neonatal morbidity and mortality when administered to pregnant women. When pregnancy is detected, CILAZAPRIL should be discontinued as soon as possible.

The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function, associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development.

Prematurity, and patent ductus arteriosus and other structural cardiac malformations, as well as neurologic malformations, have also been reported following exposure in the first trimester of pregnancy.

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.

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.

Nursing Women

The presence of concentrations of ACE inhibitor have been reported in human milk. Use of ACE inhibitors is not recommended during breast-feeding.

PRECAUTIONS

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-aldersterone system, such as patients with bilateral renal artery stenosis, unilateral renal artery stenosis to a solitary kidney, or severe congestive heart failure, treatment with agents that inhibit this sytem has been associated with oliguria, progressive azotemia, and rarely, acute renal failure and/or death. In susceptible patients, concomitant diuretic use may further increase risk.

Use of CILAZAPRIL (cilazapril) should include appropriate assessment of renal function.

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.

Anaphylactoid Reactions during Membrane Exposure

Anaphylactoid reactions have been reported in patients dialysed with high-flux membranes (e.g., polyacrylonitrile [PAN]) 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 LDL Apheresis

Rarely, patients receiving ACE inhibitors during low density lipoprotein (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 isolated 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 therefore be interrupted before the start of desensitization therapy. In this situation, cilazapril must not be replaced by a beta-blocker.

Hyperkalemia

In clinical trials, elevated serum potassium (greater than 5.5 mEq/L) was observed in approximately 0.7% of hypertensive patients and 0.8% of congestive heart failure patients receiving cilazapril. In most cases these were isolated values which resolved despite continued therapy, however in one case the patient discontinued treatment. 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 and ADVERSE REACTIONS).

Valvular Stenosis

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

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.

Diabetes

Administration of ACE inhibitors in patients with diabetes may potentiate the blood glucose lowering effect of oral hypoglycemic agents or insulin.

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.

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

Elevations of liver enzymes and/or serum bilirubin have been reported for cilazapril (see ADVERSE REACTIONS). Jaundice was also spontaneously reported in one patient worldwide. Should the patient receiving CILAZAPRIL experience any symptoms of jaundice particularly during the first weeks or months of treatment, it is recommended that a full set of liver function tests and any other necessary investigation be carried out. Discontinuation of CILAZAPRIL should be considered when appropriate.

There are no adequate studies in patients with cirrhosis and/or liver dysfunction. Cilazapril 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.

Cough

A dry, persistent cough, which usually disappears only after withdrawal or lowering of the dose of cilazapril, has been reported.

Such possibility should be considered as part of the differential diagnosis of the cough.

Pediatric Use

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

Use in Elderly

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. In elderly patients with congestive heart failure on high diuretic dosage, the recommended starting dose of cilazapril 0.5 mg must be strictly followed (see WARNINGS, Hypotension, and DOSAGE AND ADMINISTRATION).

Drug Interactions

Diuretic Therapy: Patients concomitantly taking ACE inhibitors and diuretics, and especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy. The possibility of hypotensive effects after the first dose of cilazapril can be minimized by either discontinuing the diuretic, or increasing the salt intake prior to initiation of treatment with CILAZAPRIL. If it is not possible to discontinue the diuretic, the starting dose of CILAZAPRIL should be reduced and the patient should be closely observed for several hours following initial dose and until blood pressure has stabilized (see WARNINGS and DOSAGE AND ADMINISTRATION).

Agents Increasing Serum Potassium: Since cilazapril decreases aldosterone production, elevation of serum potassium may occur. Potassium sparing diuretics such as spironolactone, triamterene or amiloride, or potassium supplements should be given only for documented hypokalemia and with caution since they may lead to a significant increase in serum potassium particularly in patients with renal impairment. Therefore, if concomitant use for such agents is indicated, their dosage should be reduced when CILAZAPRIL is initiated and serum potassium and renal function should be monitored carefully. Salt substitutes containing potassium should also be used with caution.

Agents Causing Renin Release: The antihypertensive effect of cilazapril is augmented by antihypertensive agents that cause renin release (e.g., diuretics).

Agents Affecting Sympathetic Activity: Agents affecting sympathetic activity (e.g., ganglionic blocking agents or adrenergic neuron blocking agents) should be used with caution. Beta-adrenergic blocking drugs may add some further antihypertensive effect to cilazapril.

Inhibitors of Endogenous Prostaglandin Synthesis: Concomitant administration of a non-steroidal anti-inflammatory drug (NSAID) may reduce the antihypertensive effect of CILAZAPRIL. 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.

Digoxin: 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).

Lithium Salts: As with other drugs which eliminate sodium, lithium elimination may be reduced. Therefore, the serum lithium levels should be monitored carefully if lithium salts are to be administered.

INFORMATION FOR PATIENTS

Pregnancy: Since the use of ACE inhibitors during pregnancy can cause injury and even death of the developing fetus, patients should be advised to stop the medication and report promptly to their physician if they become pregnant.

Angioedema: Angioedema, including laryngeal edema, may occur especially following the first dose of cilazapril. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in breathing) and to take no more drug until they have consulted with the prescribing physician. Should the tongue and/or larynx be involved, the physician should be consulted immediately.

Hypotension: Patients should be cautioned to report light-headedness, especially during the first few days of CILAZAPRIL therapy. If actual syncope occurs, the patients should be told to discontinue the drug until they have consulted with the prescribing physician.

All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure; patients should be advised to consult with their physician.

Neutropenia: Patients should be advised to report promptly any indication of infection (e.g., sore throat, fever) since this may be an early sign of neutropenia.

Impaired Liver Function: Patients should be advised to return to the physician if he/she experiences any symptoms possibly related to liver dysfunction. This would include “viral-like symptoms” in the first weeks to months of therapy (such as fever, malaise, muscle pain, rash or adenopathy which are possible indicators of hypersensitivity reactions), or if abdominal pain, nausea or vomiting, loss of appetite, jaundice, itching or any other unexplained symptoms occur during therapy.

Hyperkalemia: Patients should be advised not to use potassium supplements or salt substitutes containing potassium without consulting their physician.

Surgery: Patients planning to undergo surgery and/or anesthesia should be told to inform their physician that they are taking an ACE inhibitor.

Nursing Mothers: Patients should be advised not to breast feed if they are taking CILAZAPRIL.

ADVERSE REACTIONS

Cilazapril has been evaluated for safety in 5,450 patients treated for essential hypertension and 1,106 patients treated for congestive heart failure.

Of these, 2,586 hypertensive and 900 congestive heart failure patients were treated with cilazapril in controlled clinical trials. Cilazapril was evaluated for long-term safety in 798 hypertensive and 264 congestive heart failure patients treated for one year or longer.

The most serious adverse reactions reported in the 5,450 patients treated with cilazapril for hypertension included: angioedema/face edema (0.1%) (see WARNINGS, Angioedema), postural hypotension (0.3%), orthostatic hypotension (2.1%), myocardial infarction (0.1%), cerebrovascular disorder (0.04%), renal failure (0.09%), and thrombocytopenic purpura (0.02%).

In the 1,106 patients treated with cilazapril for congestive heart failure, the most serious adverse reactions were: postural hypotension (1.6%), symptomatic hypotension (1.2%), myocardial infarction (0.3%), renal failure (0.1%) (see PRECAUTIONS, Renal Impairment), and cardiogenic shock (1 patient) (see WARNINGS, Hypotension).

Hypotension and syncope, each reported in 0.1% of the hypertensive patients treated with cilazapril, were reported in 2.1% and 0.8% of the congestive heart failure patients treated with cilazapril.

Discontinuation of therapy was required in 63 (2.4%) of the hypertensive patients and 143 (12.9%) of the congestive heart failure patients.

The most frequent adverse reactions reported in controlled clinical trials (> 1% and more frequent than in placebo treated patients) were:

	Hypertension n=2586	Congestive Heart Failure n=900
headache	5.1%	3.2%
dizziness	3.0%	8.2%
fatigue	2.1%	2.6%
cough	1.8%	7.5%
nausea	1.3%	2.9%
asthenia	0.3%	1.6%
palpitation	0.2%	1.2%

Other adverse reactions occurring in less than 1% of the 5,450 hypertension patients and the 1,106 congestive heart failure patients treated with cilazapril were:

Cardiovascular: Chest pain, angina pectoris, tachycardia, atrial fibrillation, arrhythmia, flushing.

In the patient population treated with cilazapril for congestive heart failure, there were reports of bradycardia, AV block, extra systoles, cardiac failure and cardiac decompensation.

Renal: Micturition frequency, polyuria, dysuria, uremia, renal pain.

Hematologic: Epistaxis, anemia, purpura.

Gastrointestinal: Dyspepsia, abdominal pain, diarrhea, constipation, vomiting, flatulence, GI bleeding, rectum bleeding, anorexia.

Dermatologic/Allergic: Rash (includes maculo-papular rash and erythematous rash), dermatitis, pruritus, urticaria, angioedema (including face edema).

Nervous System: Increased sweating, paresthesia, hypoesthesia, impotence, decreased libido, depression, anxiety, dry mouth, vertigo, migraine, tremor, dysphonia, ataxia, confusion, somnolence, insomnia, nervousness.

Musculoskeletal: Myalgia, leg cramps, arthralgia.

Special Senses: Tinnitus, abnormal vision, photophobia, conjunctivitis, taste perversion.

Respiratory: Rhinitis, sinusitis, pharyngitis, bronchitis, respiratory tract infection, dyspnea, bronchospasm.

In the congestive heart failure patient database the overall incidence of dyspnea was 3.1%. Dyspnea however was less frequent after cilazapril than after placebo.

Metabolic: Gout.

Body as a Whole: Malaise, hot flushes, pain, edema, rigors.

Postmarketing Experience: Treatment with ACE inhibitors has been associated with, rarely, the following: hemolytic anemia, pemphigus and Stevens-Johnson syndrome. As for other ACE inhibitors, isolated cases of pancreatitis, in some cases fatal, have been reported in patients treated with cilazapril.

ABNORMAL LABORATORY FINDINGS

Hematology:
Patients had clinically relevant changes in platelet (0.4% and 0.7%), neutrophil (1.9% and 1.4%) or white blood cell counts (1.3% and 0.7%) while treated for hypertension and congestive heart failure respectively.

Leucopenia and neutropenia: Leucopenia was observed in 0.2% (10/3,580) and 0% (0/1,163) and neutropenia in 0.4% (22/5,720) and 0.6% (7/1,163) of the hypertensive and congestive heart failure patients respectively. Most of these were single transient occurrences; one case with two successive abnormalities showed no associated clinical symptoms.

Liver Function Tests:
Clinically relevant changes in the values associated with liver function (SGOT, SGPT, GGTP, LDH, total bilirubin and alkaline phosphatase) occurred in 0.1% (bilirubin) to 1.1% (SGPT, GGTP) of the hypertensive patients and in 0.8% (LDH) to 2.9% (SGPT) of the congestive heart failure patients. Most of these abnormalities were transient. See PRECAUTIONS, Patients with Impaired Liver Function.

Renal:
Clinically relevant changes in renal function test results (BUN or serum creatinine concentrations) occurred in 0.6% or less of the hypertensive patients and in 2.6% and 0.9% respectively of the congestive heart failure patients.

Hyperkalemia: (see PRECAUTIONS)

Creatinine: Serum creatinine values > 2 mg/dL were reported in 1.3% (44/3,468) of the hypertensive patients. Two thirds of these patients had renal impairment at baseline. Serum creatinine values >2.8 mg/dL were reported in 0.4% (5/1,163) of the congestive heart failure patients. Of these, four of the five had abnormal serum creatinine values at baseline.

Proteinuria (≥2+ dipstick reaction or excretion of ≥ 1 g/24h): Proteinuria considered remotely, possibly or probably related to therapy was reported in 0.5% (17/3,421) of the hypertensive patients. Five patients had prior renal impairment. In congestive heart failure patients, 1.4% (16/1,106) experienced potentially clinically relevant proteinuria.

Other: In congestive heart failure patients, hyperglycemia considered remotely, possibly or probably related to therapy was reported in 0.2% (2/1,106) patients.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Limited data are available with regard to overdosage in humans. The most likely clinical manifestation would be symptoms attributable to severe hypotension, which should be normally treated by intravenous volume expansion with normal saline.

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

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

DOSAGE AND ADMINISTRATION

Dosage of CILAZAPRIL (cilazapril) must be individualized.

Initiation of therapy requires consideration of recent antihypertensive drug treatment, the extent of blood pressure elevation, salt restriction, and other pertinent clinical factors. The dosage of other antihypertensive agents being used with CILAZAPRIL may need to be adjusted.

The dose should always be taken at about the same time each day.

Hypertension:

Monotherapy*:*

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

In most patients, the antihypertensive effect of CILAZAPRIL is maintained with a once a day 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 CILAZAPRIL 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 CILAZAPRIL.

Concomitant Diuretic Therapy:

In patients receiving diuretics, CILAZAPRIL 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 CILAZAPRIL to reduce the likelihood of hypotension (see WARNINGS). If this is not possible because of the patient's condition, CILAZAPRIL 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)

CILAZAPRIL 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 CILAZAPRIL must be adjusted according to individual tolerability, response, and clinical status.

Dosage Adjustment in Renal Impairment

(see PRECAUTIONS, Anaphylactoid Reactions during Membrane Exposure)

The following dose schedules are recommended in patients with hypertension:

Creatinine Clearance	Initial Dose of CILAZAPRIL	Maximal Dose of CILAZAPRIL
> 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	0.25-0.5 mg once or twice a week according to blood pressure response	

Hemodialysis patients: CILAZAPRIL should be administered on days when dialysis is not performed and the dosage should be adjusted according to blood pressure response.

Dosage Adjustment in Hepatic Impairment

Should patients with liver cirrhosis require treatment with cilazapril, treatment should be initiated with caution at a dose of 0.5 mg once daily or less as significant hypotension may occur (see PRECAUTIONS).

Congestive Heart Failure

CILAZAPRIL can be used as adjunctive therapy with digitalis and/or diuretics in patients with congestive heart failure. Therapy should be initiated under close medical supervision. Blood pressure and renal function should be monitored both before and during treatment with cilazapril because severe hypotention and more rarely, renal failure have been reported (see WARNINGS and PRECAUTIONS).

Initiation of therapy requires consideration of recent diuretic therapy and the possibility of severe salt/volume depletion. If possible, the dose of diuretic should be reduced before beginning treatment, to reduce the likelihood of hypotention. Serum potassium should also be monitored (see WARNINGS and PRECAUTIONS, Drug Interactions).

Therapy with cilazapril should be initiated with a recommended starting dose of 0.5 mg once daily under close medical surpervision. **In elderly patients with congestive heart failure on high diuretic dosage the recommended starting dose of cilazapril 0.5 mg must be strictly followed (see WARNINGS).**

The dose should be increased to the lowest maintenance dose of 1 mg daily, usually within a 5 day period, according to tolerability and clinical status. Further titration within the usual maintenance dose of 1 mg to 2.5 mg daily should be carried out based on patients response, clinical status and tolerability.

The usual maximum dose is *2.5* mg once daily. A few patients have been titrated to 5 mg once daily with some additional benefits being achieved. However only limited data is available in congestive heart failure patients treated with 5 mg once daily.

Dosage Adjustment in Patients with Congestive Heart Failure and Renal Impairment or Hyponatremia:

Reduced dosage may be required for patients with congestive heart failure and renal impairment or hyponatremia depending on the creatinine clearance. The following dosing is recommended:

Creatinine Clearance	**Initial Dose of CILAZAPRIL**	
> 40 mL/min	0.5 mg once daily	2.5 mg once daily
10-40 mL/min	0.25 - 0.5 mg once daily	2.5 mg once daily
< 10 mL/min	0.25-0.5 mg once or twice a week according to blood pressure response	

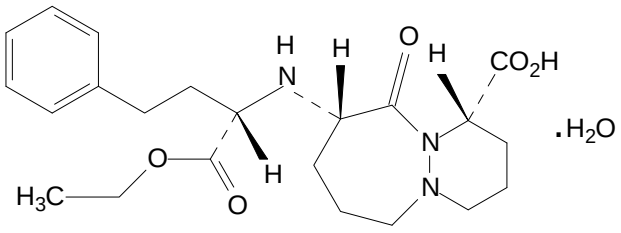
PHARMACEUTICAL INFORMATION

Drug Substance:

Proper Name: cilazapril monohydrate

Chemical Name: (1S-9S)-9-[[(1S-1-(ethoxycarbonyl)-3-phenylpropyl]amino]-10-oxooctahydro-6H-pyridazino[1,2-a][1,2]-diazepine-1-carboxylic acid monohydrate

Structural Formula:



MolecularFormula: $C_{22}H_{31}N_3O_5$, H_2O

Molecular Weight: 435.5

Physical Form: A white or almost white, crystalline powder

Solubility: Slightly soluble in water, freely soluble in methanol and in methylene chloride.

Pka: 3.3, 6.5

pH (1 % suspension): 4.99

Partition Coefficient: 0.65 (octanol/water)

Melting Point: 95-97ºC

Composition

CILAZAPRIL 1 mg film coated tablets contain 1 mg anhydrous cilazapril, as cilazapril monohydrate and the following non-medicinal ingredients: lactose, cornstarch, microcrystalline cellulose, talc, sodium stearyl fumarate, hypromellose, titanium dioxide, macrogol, iron oxide yellow and polysorbate.

CILAZAPRIL 2.5 mg film-coated tablets contain 2.5 mg anhydrous cilazapril, as cilazapril monohydrate and the following non-medicinal ingredients: lactose, cornstarch, microcrystalline cellulose, talc, sodium stearyl fumarate, hypromellose, titanium dioxide, macrogol and iron oxide red.

CILAZAPRIL 5 mg film-coated tablets contain 5 mg anhydrous cilazapril, as cilazapril monohydrate and the following non-medicinal ingredients: lactose, cornstarch, microcrystalline cellulose, talc, sodium stearyl fumarate, polydextrose, hypromellose, titanium dioxide, glycerol, triacetate, macrogol, and iron oxide red and yellow.

Stability and Storage Recommendations

Store 15-25 ºC. Keep container tightly closed. Protect from moisture.

AVAILABILITY OF DOSAGE FORMS

CILAZAPRIL 1 mg: Yellow, oval shaped biconvex film coated tablets engraved with N bisect N on one side and 1 on the other side. Available in bottles of 100 tablets.

CILAZAPRIL 2.5 mg: Pinkish-brown, oval shaped biconvex film coated tablets engraved with N bisect N on one side and 2.5 on the other side. Available in bottles of 100 tablets.

CILAZAPRIL 5 mg: Reddish-brown, oval shaped biconvex film coated tablets engraved with N bisect N on one side and 5 on the other side. Available in bottles of 100 tablets.

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 µM) 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 below:

Animal Model	Cilazapril Activity	
Conscious normotensive rats	ED_{50} 0.02 mg/kg p.o. (at 60 min)	—
Anesthetised SHAD (unilaterally adrenalectomised and contralaterally adrenal demedulated SHR) rats	ED_{50} 0.44 µmol/kg i.v.	ED_{50} 0.06 µmol/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.
Anesthetised normotensive dogs	ED_{50} 0.035 mg/kg i.v (0.084 µmol/kg)	—

In the anesthetised SHAD rats 0.06 µmol/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.

TOXICOLOGY

ACUTE TOXICITY

Species	Sex	Route	Approximate LD_{50} (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.

Long-Term Toxicity

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).
Rat (16M + 16F)	4 Weeks	25, 125, 625	p.o.	All dose groups: Salivation; slight reduction in motor activity; increased urine volumes and minimal decreases in specific gravity (males). 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). 625 mg/kg/day: Increased BUN values (1.5x) (males); decreased BMC[1] (males); slight decrease in heart and liver (males) weight.

[1] Bone marrow nucleated cell count.

Long-Term Toxicity (Cont'd)

SPECIES (#/group)	STUDY DURATION	DOSE ADMINISTRATION (mg/kg/day)	ROUTE	FINDINGS
Monkey Marmoset (3/6M + 3F)	4 Weeks	0, 5, 15, 50	p.o.	15 and 50 mg/kg/day: Marginal decreases in RBC, Hb and PCV values. 50 mg/kg/day: Increase in plasma urea (2x), K+ and cholesterol values; increased incidence of kidney tubule cells in urine.
Rat (16M + 16F)	13 Weeks	0, 10, 50, 250	p.o.	All dose groups: Very slight increases in urine volume and decreased SG values (males). 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). 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).
Monkey Cynomolgus (4M + 4F)	13 weeks	0, 2.5, 25, 50	p.o.	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. 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.
Monkey Baboon (2M + 2F)	13 Weeks	0, 2, 10, 20, 40	p.o.	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). 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.

Long-Term Toxicity (Cont'd)

SPECIES (#/group)	STUDY DURATION	DOSE ADMINISTRATION (mg/kg/day)	ROUTE	FINDINGS
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.	All dose groups: Slight decrease in heart rate; weight loss; lethargy; hunched posture. Pilo-rection; facial fur-staining; dose-related increases in kidney weights (male). 12 and 50 mg/kg/day: Hypertrophy of afferent glomerular arterioles in the kidneys (13 weeks). 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).
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.

Long-Term Toxicity (Cont'd)

SPECIES (#/group)	STUDY DURATION	DOSE ADMINISTRATION (mg/kg/day)	ROUTE	FINDINGS
Rat (35M + 35F)	78 Weeks	0, 0.5, 4, 40	p.o.	All dose levels: Small reductions in body weight gain. 4 and 40 mg/kg/day: Slight decrease in RBC, PCV and Hb; minimal reduction in food intake; increase in BUN (2x) (males). 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.

Reproduction and Teratology

SPECIES #/GROUP	DOSE (mg/kg/day)	ROUTE	DURATION OF DOSING	EFFECTS
Fertility and General Reproduction Performance				
Rat Charles River (Crl: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.

Reproduction and Teratology (Cont'd)

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 (CDCrl: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.

CARCINOGENICITY

An eighty-eight 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. Tri-PAs staining of kidney sections from the 104 week rat carcinogenicity study indicated no hyperplastic or neoplastic oxyphilic cell response and no enhancement of the development of oncocytomas.

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 µcg/mL), unscheduled DNA synthesis assay (up to 200 µcg/mL), mutagenic assay with Chinese hamster V79 cells with or without metabolic activation (up to 4,800 µcg/mL), chromosomal abbreration test with or without metabolic activation (up to 3,500 µcg/mL), or in vivo micronucleus test in mice (2.0 g/kg).

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29. Product Monograph for Inhibace® by Hoffmann-La Roche Limited, Mississauga, Ontario, Canada. Date of Revision: June 20, 2007.

29. A comparative two-way crossover bioavailability study was performed on two cilazapril tablets, Cilazapril 5 mg film-coated tablets and Inhibace® 5 mg tablets, under fasting conditions.