PRODUCT MONOGRAPH

[Pr]NU-LISINOPRIL/HCTZ

Lisinopril and Hydrochlorothiazide Tablets

10/12.5 mg, 20/12.5 mg and 20/25 mg

Angiotensin Converting Enzyme Inhibitor/Diuretic

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PRODUCT MONOGRAPH

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THERAPEUTIC CLASSIFICATION

Angiotensin Converting Enzyme Inhibitor/Diuretic

ACTION AND CLINICAL PHARMACOLOGY

NU-LISINOPRIL /HCTZ (lisinopril and hydrochlorothiazide) combines the action of an angiotensin converting enzyme inhibitor, lisinopril, and a diuretic, hydrochlorothiazide.

Lisinopril

Angiotensin converting enzyme (ACE) is a peptidyl dipeptidase which catalyzes the conversion of angiotensin I to the pressor substance, angiotensin II. Inhibition of ACE results in decreased plasma angiotensin II, which leads to increased plasma renin activity (due to removal of negative feedback of renin release) and decreased aldosterone secretion. Although the latter decrease is small, it results in a small increase in serum potassium. In patients treated with lisinopril plus a thiazide diuretic, there was essentially no change in serum potassium (see PRECAUTIONS). ACE is identical to kininase II. Thus, lisinopril may also block the degradation of bradykinin, a potent vasodilator peptide. However, the role that this plays in the therapeutic effects of lisinopril is unknown.

While the mechanism through which lisinopril lowers blood pressure is believed to be primarily the suppression of the renin-angiotensin-aldosterone system, lisinopril also lowers blood pressure in patients with low-renin hypertension. However, black hypertensive patients (usually a low-renin hypertensive population) have a smaller average response to lisinopril monotherapy than non-black patients.

When lisinopril is given together with thiazide-type diuretics, its blood pressure lowering effect is approximately additive.

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 predominantly a saluretic agent, *in vitro* studies have shown that it has a carbonic anhydrase inhibitory action which seems to be relatively specific for the renal tubular mechanism. It does not appear to be concentrated in erythrocytes or the brain in sufficient amounts to influence the activity of carbonic anhydrase in those tissues.

Hydrochlorothiazide is useful in the treatment of hypertension. It may be used alone or as an adjunct to other antihypertensive drugs. Hydrochlorothiazide does not affect normal blood pressure. The mechanism of its antihypertensive action is not known. Lowering of the sodium content of arteriolar smooth muscle cells and diminished response to norepinephrine have been postulated.

Pharmacokinetics

Lisinopril

Following oral administration of lisinopril, peak serum concentrations occur within about 7 hours. Declining serum concentrations exhibit a prolonged terminal phase which does not contribute to drug accumulation. This terminal phase probably represents saturable binding to ACE and is not proportional to dose. Lisinopril does not bind to plasma proteins other than ACE.

Lisinopril does not undergo metabolism and is excreted unchanged entirely in the urine. Based on urinary recovery, the extent of absorption of lisinopril is approximately 25%, with large inter-subject variability (6-60%) at all doses tested (5-80 mg).

Lisinopril absorption is not influenced by the presence of food in the gastrointestinal tract.

Upon multiple dosing, lisinopril exhibits an effective half-life of accumulation of 12 hours.

In a study in elderly healthy subjects (65 years and above), a single dose of lisinopril 20 mg produced higher serum concentrations and higher values for the area under the plasma curve than those seen in young healthy adults given a similar dose. In another study, single daily doses of lisinopril 5 mg were given for 7 consecutive days to young and elderly healthy volunteers.

Maximum serum concentrations of lisinopril on Day 7 were higher in the elderly volunteers than in the young.

Impaired renal function decreases elimination of lisinopril. This decrease becomes clinically important when the glomerular filtration rate is below 30 mL/min. (See PRECAUTIONS - Patients with Impaired Renal Function, and DOSAGE AND ADMINISTRATION).

Lisinopril can be removed by dialysis.

Studies in rats indicate that lisinopril crosses the blood-brain barrier poorly.

Hydrochlorothiazide

Hydrochlorothiazide is not metabolized but is eliminated rapidly by the kidney. The plasma half-life is 5.6-14.8 hours when the plasma levels can be followed for at least 24 hours. At least 61% of the oral dose is eliminated unchanged within 24 hours. Hydrochlorothiazide crosses the placental but not the blood-brain barrier and is excreted in breast milk.

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.

Lisinopril - Hydrochlorothiazide

Concomitant administration of lisinopril 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.

Pharmacodynamics

Lisinopril

Administration of lisinopril to patients with hypertension results in a reduction of both supine and standing blood pressure. Abrupt withdrawal of lisinopril has not been associated with a rapid increase in blood pressure. In most patients studied, after oral administration of an individual dose of lisinopril, the onset of antihypertensive activity is seen at one hour with peak reduction of blood pressure achieved by 6 hours. Although an antihypertensive effect was observed 24 hours after dosing with recommended single daily doses, the effect was more consistent and the mean effect was considerably larger in some studies with doses of 20 mg or more than with

lower doses. However, at all doses studied, the mean antihypertensive effect was substantially smaller 24 hours after dosing than it was 6 hours after dosing. On occasion, achievement of optimal blood pressure reduction may require 2 to 4 weeks of therapy.

In hemodynamic studies in patients with essential hypertension, blood pressure reduction was accompanied by a reduction in peripheral arterial resistance with little or no change in cardiac output and in heart rate. In a study in nine hypertensive patients, following administration of lisinopril, there was an increase in mean renal blood flow that was not significant. Data from several small studies are inconsistent with respect to the effect of lisinopril on glomerular filtration rate in hypertensive patients with normal renal function, but suggest that changes, if any, are not large.

Comparative Bioavailability:

A comparative bioavailability study was performed on healthy human volunteers under fasting conditions. The rate and extent of absorption of lisinopril and hydrocholorothiazide following a single oral dose of NU-LISINOPRIL /HCTZ (lisinopril and hydrochlorothiazide) or ZESTORETIC tablets were measured and compared. Since the NU-LISINOPRIL /HCTZ 10/12.5 mg tablets are considered to be pharmaceutically identical to the NU-LISINOPRIL /HCTZ 20/25 mg tablets, the *in-vivo* performance of the 10/12.5 mg tablet is supported by the comparative bioavailability data for the 20/25 mg tablet present below.

The results from measured data are summarized as follows:

Summary Table of the Comparative Bioavailability Data Lisinopril/Hydrochlorothiazide (Dose: 1 x 20/25 mg) From Measured Data - Under Fasting Conditions Based on Lisinopril				
Parameter	Geometric Mean Arithmetic Mean (CV%)		Ratio of Geometric Means (%)**	90% Confidence Interval
	Nu-Lisinopril /HCTZ	Zestoretic®†		
AUC_{0-72} (ng.h/mL)	1228 1347 (41)	1334 1402 (31)	92.1	83.3 - 101.8
AUC_I (ng.h/mL)	1322 1439 (40)	1412 1472 (29)	92.0	83.5 - 101.3
C_{MAX} (ng/mL)	90.8 103 (47)	99.7 106 (33)	91.1	81.4 - 101.9
T_{MAX}* (h)	7.05 (15)	6.96 (11)	--	--
$T_{½}$* (h)	27.4 (35)	26.7 (36)	--	--

* Arithmetic means (CV%).
** Based on the least squares estimate.
† Zestoretic® is marketed by AstraZeneca Canada Inc., and was purchased in Canada.

Summary Table of the Comparative Bioavailability Data Lisinopril/Hydrochlorothiazide (Dose: 1 x 20/25 mg) From Measured Data - Under Fasting Conditions Based on Hydrochlorothiazide				
Parameter	Geometric Mean Arithmetic Mean (CV%)		Ratio of Geometric Means (%)**	90% Confidence Interval
	Nu-Lisinopril /HCTZ	Zestoretic®†		
AUC_T (ng.h/mL)	876 905 (26)	918 942 (25)	95.5	90.9 - 100.2
AUC_I (ng.h/mL)	928 956 (25)	972 999 (25)	95.5	91.2 - 100.0
C_{MAX} (ng/mL)	128 133 (28)	137 141 (25)	93.3	88.6 - 98.3
T_{MAX}* (h)	2.74 (39)	2.34 (32)	--	--
$T_{½}$* (h)	10.0 (17)	10.2 (11)	--	--

* Arithmetic means (CV%).
** Based on the least squares estimate.
† Zestoretic® is marketed by AstraZeneca Canada Inc., and was purchased in Canada.

Summary Table of the Comparative Bioavailability Data Lisinopril/Hydrochlorothiazide (Dose: 2 x 20/12.5 mg) From Measured Data - Under Fasting Conditions Based on Lisinopril				
Parameter	Geometric Mean Arithmetic Mean (CV%)		Ratio of Geometric Means (%)**	90% Confidence Interval
	Nu-Lisinopril /HCTZ	Zestoretic®†		
AUC_{0-72} (ng.h/mL)	2240 2375 (33)	2546 2700 (34)	88.0	80.7 - 95.9
AUC_I (ng.h/mL)	2322 2448 (31)	2615 2765 (33)	88.8	81.9 - 96.3
C_{MAX} (ng/mL)	176 188 (34)	196 209 (35)	89.8	81.9 - 98.6
T_{MAX}* (h)	6.29 (15)	6.64 (17)	--	--
$T_{½}$* (h)	25.3 (41)	22.1 (27)	--	--

* Arithmetic means (CV%).
** Based on the least squares estimate.
† Zestoretic® is marketed by AstraZeneca Canada Inc., and was purchased in Canada.

Summary Table of the Comparative Bioavailability Data Lisinopril/Hydrochlorothiazide (Dose: 2 x 20/12.5 mg) From Measured Data - Under Fasting Conditions Based on Hydrochlorothiazide				
Parameter	Geometric Mean Arithmetic Mean (CV%)		Ratio of Geometric Means (%)**	90% Confidence Interval
	Nu-Lisinopril /HCTZ	Zestoretic®†		
AUC_T (ng.h/mL)	899 923 (22)	945 967 (23)	95.1	91.3 - 99.0
AUC_I (ng.h/mL)	952 978 (23)	998 1022 (23)	95.4	91.9 - 99.1
C_{MAX} (ng/mL)	136 142 (30)	142 147 (29)	95.6	86.9 - 105.2
T_{MAX}* (h)	2.55 (47)	2.21 (54)	--	--
$T_{½}$* (h)	9.94 (14)	9.77 (12)	--	--

* Arithmetic means (CV%).
** Based on the least squares estimate.
† Zestoretic® is marketed by AstraZeneca Canada Inc., and was purchased in Canada.

INDICATIONS AND CLINICAL USE

NU-LISINOPRIL /HCTZ (lisinopril and hydrochlorothiazide) is indicated for the treatment of essential hypertension in patients for whom combination therapy is appropriate.

In using NU-LISINOPRIL /HCTZ, consideration should be given to the risk of angioedema (see WARNINGS - Angioedema).

Lisinopril 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.

NU-LISINOPRIL /HCTZ is not indicated for initial therapy. Patients in whom lisinopril and diuretic are initiated simultaneously can develop symptomatic hypotension (see PRECAUTIONS - Drug Interactions).

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

CONTRAINDICATIONS

NU-LISINOPRIL /HCTZ (lisinopril and hydrochlorothiazide) is contraindicated in patients who:

- are hypersensitive to any component of this product,
- have a known allergy to angiotensin converting enzyme inhibitors,
- have a history of angioneurotic edema relating to previous treatment with an
- angiotensin converting enzyme inhibitor,
- have hereditary or idiopathic angioneurotic edema, and because of the hydrochlorothiazide component, in patients who have anuria,
- hypersensitivity to other sulfonamide-derived drugs.

WARNINGS

Serious Warnings and Precautions

When used in pregnancy, ACE inhibitors can cause injury or even death of the developing fetus. When pregnancy is detected NU-LISINOPRIL /HCTZ should be discontinued as soon as possible (see WARNINGS - Use in Pregnancy, and Information For Patients).

Angioedema

Angioedema has been reported in patients treated with lisinopril/ hydrochlorothiazide and may occur at anytime during therapy. Angioedema associated with laryngeal edema and/or shock may be fatal. If angioedema occurs, NU-LISINOPRIL /HCTZ should be promptly discontinued and the patient should be treated, and observed until the swelling subsides. Where swelling is confined only to the tongue, without respiratory distress, patients may require prolonged observation since treatment with antihistamines and corticosteroids may not be sufficient.

However, where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, and especially in cases where there has been a history of airway surgery, emergency therapy should be administered promptly when indicated. This includes giving subcutaneous adrenaline/epinephrine (0.5 mL 1:1000) and/or maintaining a patent airway. The patient should be under close medical supervision until the complete and sustained symptom resolution has occurred.

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 increased risk of angioedema while receiving an ACE inhibitor (see CONTRAINDICATIONS).

Hypotension

Symptomatic hypotension has occurred after administration of lisinopril, usually after the first or second dose or when the dose was increased. It is more likely to occur in patients who are volume depleted by diuretic therapy, dietary salt restriction, dialysis, diarrhea, or vomiting. Therefore, NU-LISINOPRIL /HCTZ should not be used to start therapy or when a dose change is needed. Severe hypotension is also a risk in renin-dependant renovascular hypertension;

NU-LISINOPRIL /HCTZ is not indicated for this condition (see INDICATIONS AND CLINICAL USE). In patients with ischemic heart or cerebrovascular disease, an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident (see ADVERSE REACTIONS). Because blood pressure could potentially fall, patients at risk for hypotension should start lisinopril therapy under very close medical supervision, usually in a hospital. Such patients should be followed closely for the first two weeks of treatment and whenever the dose of lisinopril and/or hydrochlorothiazide is increased. In patients with severe congestive heart failure, with or without associated renal insufficiency, excessive hypotension has been observed and may be associated with oliguria and/or progressive azotemia, and rarely with 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 may not be a contraindication to further doses. These can usually be given to hypertensive patients without difficulty once the blood pressure has increased after volume expansion. Re-institution of therapy at reduced dosages, or re-institution with either component alone, should be considered.

Neutropenia/Agranulocytosis

Agranulocytosis and bone marrow depression have been caused by angiotensin converting enzyme inhibitors. Several cases of agranulocytosis and neutropenia have been reported in which a causal relationship to lisinopril cannot be excluded. Current experience with the drug shows the incidence to be rare. Periodic monitoring of white blood cell counts should be considered, especially in patients with collagen vascular disease and renal disease.

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.

Patients with Impaired Liver Function

Hepatitis (with very rare progression to hepatic failure), jaundice (hepatocellular and/or cholestatic), elevations of liver enzymes and/or serum bilirubin have occurred during therapy

with lisinopril in patients with or without pre-existing liver abnormalities. In most cases the changes were reversed on discontinuation of the drug and appropriate medical follow up.

Should the patient receiving NU-LISINOPRIL /HCTZ experience any unexplained symptoms (see PRECAUTIONS - Information For Patients), 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 NU-LISINOPRIL /HCTZ should be considered when appropriate.

There are no adequate studies in patients with cirrhosis and/or liver dysfunction. NU-LISINOPRIL /HCTZ 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.

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

Hypersensitivity Reactions

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

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

Use in Pregnancy

ACE inhibitors can cause fetal and neonatal morbidity and mortality when administered to pregnant women. When pregnancy is detected, NU-LISINOPRIL /HCTZ 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, experience with those procedures has not been associated with significant clinical benefit.

Lisinopril has been removed from the neonatal circulation by peritoneal dialysis.

Animal Data

Lisinopril was not teratogenic in mice treated on days 6-15 of gestation with up to 1000 mg/kg/day (625 times the maximum recommended human dose). There was an increase in fetal resorptions at doses down to 100 mg/kg; at doses of 1000 mg/kg, this was prevented by saline supplementation. There was no fetotoxicity or teratogenicity in rats treated with up to 300 mg/kg/day (188 times the maximum recommended dose) of lisinopril at days 6-17 of gestation. In rats receiving lisinopril from day 15 of gestation through day 21 postpartum, there was an increased incidence in pup deaths on days 2-7 postpartum and a lower average body weight of pups on day 21 postpartum. The increase in pup deaths and decrease in pup weight did not occur with maternal saline supplementation.

Lisinopril, at doses up to 1 mg/kg/day, was not teratogenic when given throughout the organogenic period in saline supplemented rabbits. Saline supplementation (physiologic saline in place of tap water) was used to eliminate maternotoxic effects and enable evaluation of the teratogenic potential at the highest possible dosage level. The rabbit has been shown to be extremely sensitive to angiotensin converting enzyme inhibitors (captopril and enalapril) with maternal and fetotoxic effects apparent at or below the recommended therapeutic dosage levels in man.

Fetotoxicity was demonstrated in rabbits by an increase incidence of fetal resorptions at an oral dose of lisinopril of 1 mg/kg/day and by an increased incidence of incomplete ossification at the lowest dose tested (0.1 mg/kg/day). A single intravenous dose of 15 mg/kg of lisinopril administered to pregnant rabbits on gestation days 16, 21 or 26 resulted in 88% to 100% fetal death.

By whole body autoradiography, radioactivity was found in the placenta following administration of labelled lisinopril to pregnant rats, but none was found in the fetuses.

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

Use of NU-LISINOPRIL /HCTZ (lisinopril and hydrochlorothiazide) should include appropriate assessment of renal function.

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 (see DOSAGE AND ADMINISTRATION - Dosage Adjustment in Renal Impairment).

Anaphylactoid Reactions during membrane exposure

Anaphylactoid reactions have been reported in patients dialysed with high-flux membranes (e.g.: polyacrylonitrile [PAN]) and during low density lipoproteins (LDL) apheresis with dextran sulphat) 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 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.

Hyperkalemia

In clinical trials hyperkalemia (serum potassium >5.7 mEq/L) occurred in approximately 1.4% of hypertensive patients. In most cases these were isolated values which resolved despite continued therapy. Hyperkalemia was not a cause of discontinuation of therapy. Risk factors for the development of hyperkalemia may include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements and/or potassium-containing salt substitutes. (See PRECAUTIONS - Drug Interactions).

Valvular Stenosis, Hypertrophic Cardiomyopathy

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 after load reduction.

NU-LISINOPRIL /HCTZ should be given with caution to patients with aortic or hypertrophic cardiomyopathy.

Metabolism

Thiazide therapy may impair glucose tolerance. Dosage adjustment of hypoglycemic agents may be required (see PRECAUTIONS- Drug Interactions).

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

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.

Thiazides may decrease urinary calcium excretion. Thiazides may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function. Increases in cholesterol, triglyceride and glucose levels may be associated with thiazide diuretic therapy.

Surgery/Anesthesia

In patients undergoing major surgery or during anesthesia with agents that produce hypotension, lisinopril blocks angiotensin II formation, secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion. (see PRECAUTIONS - Drug Interactions).

Cough

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

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

Use in the Elderly

In general, blood pressure response and adverse experiences were similar in younger and older patients given similar doses of lisinopril. Pharmacokinetic studies, however, indicate that maximum blood levels and area under the plasma concentration time curve (AUC) are doubled in older patients so that dosage adjustments should be made with particular caution.

Use In Children

NU-LISINOPRIL /HCTZ has not been studied in children and, therefore, use in this age group is not recommended.

Occupational Hazards

Ability to drive and use machines: dizziness or tiredness may occur during treatment with NU-LISINOPRIL /HCTZ.

Drug Interactions

Hypotension - Patients on Diuretic Therapy

Patients on diuretics and especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with lisinopril. The possibility of hypotensive effects with lisinopril can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with lisinopril. (see WARNINGS, and DOSAGE AND ADMINISTRATION).

Hypotension - Patients on antihypertensive therapy

When lisinopril is given to patients already treated with other antihypertensive agents, further falls in blood pressure may occur.

Potassium Supplements, potassium-sparing agents or potassium-containing salt substitutes

Since lisinopril 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 and with frequent monitoring of serum potassium since they may lead to a significant increase in serum potassium. Salt substitutes which contain potassium should also be used with caution.

Agents Causing Renin Release

The antihypertensive effect of NU-LISINOPRIL /HCTZ 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) may be used with caution. Beta-adrenergic blocking drugs add some further antihypertensive effect to lisinopril.

Lithium

Lithium generally should not be given with diuretics or ACE inhibitors. Diuretic agents and ACE inhibitors reduce the renal clearance of lithium and add a high risk of lithium toxicity.

d-tubocurarine

Thiazide drugs may increase the responsiveness to tubocurarine.

Insulin and oral hypoglycemic agents

Insulin and oral hypoglycemic agents requirements in diabetic patients may be increased, decreased or unchanged. Previously latent diabetes mellitus may become manifest during thiazide administration (see PRECAUTIONS - Metabolism).

Alcohol, barbiturates, or narcotics

Potentiation of orthostatic hypotension may occur.

Corticosteroids, ACTH

Intensified electrolyte depletion, particularly hypokalemia may occur.

Pressor amines (e.g. norepinephrine)

Possible decreased response to pressor amines but not sufficient to preclude their use.

Non Steroidal Anti-inflammatory Drugs

In some patients, the administration of a non-steroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing and thiazide diuretics. Therefore, when NU-LISINOPRIL /HCTZ and non-steroidal anti-inflammatory agents are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained.

In some patients with compromised renal function, lisinopril co-administration with non-steroidal anti-inflammatory drugs (NSAIDS) may produce further renal function deterioration.

Indomethacin may diminish the antihypertensive efficacy of concomitantly administered lisinopril and hydrochlorothiazide.

Information For Patients

Serious Warnings and Precautions

NU-LISINOPRIL /HCTZ should not be used during pregnancy. Patients should be advised to stop the medication and contact their physician as soon as possible if they discover that they are pregnant while taking NU-LISINOPRIL /HCTZ.

Angioedema

Angioedema, including laryngeal edema, may occur during treatment with lisinopril / hydrochlorothiazide. 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.

Hypotension

Patients should be cautioned to report lightheadedness especially during the first few days of 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 told to report promptly any indication of infection (e.g., sore throat, fever) which may be a 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.

You are pregnant, breast-feeding or thinking of becoming pregnant?

Taking NU-LISINOPRIL /HCTZ during pregnancy can cause injury and even death to your baby. This medicine should not be used during pregnancy. If you become pregnant while taking NU-LISINOPRIL /HCTZ, stop the medication and report to your doctor as soon as possible. It is possible that NU-LISINOPRIL /HCTZ passes into breast milk. You should not breast-feed while taking NU-LISINOPRIL /HCTZ.

Note: As with many other drugs, certain advice to patients being treated with NU-LISINOPRIL /HCTZ is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended events.

ADVERSE REACTIONS

In clinical trials involving 930 patients, including 100 patients treated for 50 weeks or more, the most severe clinical adverse reactions were syncope (0.8%), and hypotension (1.9%). The most frequent clinical adverse reactions were: dizziness (7.5%), headache (5.2%), cough (3.9%), fatigue (3.7%) and orthostatic effects (3.2%).

Discontinuation of treatment due to adverse reactions occurred in 4.4% of patients, mainly because of dizziness, cough, fatigue or muscle cramps.

Adverse reactions that have occurred in clinical trials or in marketing experience are those which have been previously reported with lisinopril and hydrochlorothiazide when used separately for the treatment of hypertension.

Adverse reactions occurring in hypertensive patients treated with lisinopril and hydrochlorothiazide in controlled trials are shown on the following page.

Adverse Reactions in Controlled Clinical Trials
Incidence of Adverse Reactions Occurring in Patients Treated with ZESTORETIC In Controlled Clinical Trials.

	LISINOPRIL 2633 PATIENTS %	LISINOPRIL PLUS HYDROCHLOROTHIAZIDE 930 PATIENTS%
CARDIOVASCULAR	0.8	1.9
Hypotension	0.9	3.2
Orthostatic effects	1.1	1.0
Chest pain	0.2	0.8
Syncope	0.3	0.1
Angina	0.6	0.1
Edema	0.8	0.9
Palpitation	0.5	0.1
Rhythm disturbances	-	0.6
Chest discomfort		
GASTROINTESTINAL	1.8	2.5
Diarrhea	1.9	2.2
Nausea	1.1	1.4
Vomiting	0.5	1.3
Dyspepsia	0.4	0.2
Anorexia	0.2	0.3
Constipation	0.3	0.2
Flatulence	1.4	0.9
Abdominal pain	0.5	0.2
Dry Mouth		
NERVOUS SYSTEM	4.4	7.5
Dizziness	5.6	5.2
Headache	0.5	1.5
Paresthesia	0.7	0.5
Depression	0.8	0.4
Somnolence	0.3	0.2
Insomnia	0.2	0.9
Vertigo		
RESPIRATORY	3.0	3.9
Cough	0.4	0.4
Dyspnea	2.1	2.2
Upper Respiratory Infection		
DERMATOLOGIC	1.0	1.2
Rash	0.5	0.4
Pruritus	0.3	0.8
Flushing	0.1	-*
Angiodema		
MUSCULOSKETAL	0.5	2.0
Muscle cramps	0.5	0.8
Back pain	0.2	0.5
Shoulder pain		
OTHER	-	3.7
Fatigue	2.7	1.8
Asthenia	0.2	1.0
Decreased libido	0.3	0.5
Fever	0.7	1.2
Impotence	0.2	0.2
Gout		

* See lisinopril / hydrochlorothiazide (Marketing Experience Only)

Abnormal Laboratory Findings

Hypokalemia, Hyperkalemia

(see PRECAUTIONS, Hyperkalemia, and Drug Interactions).

Creatinine, Blood Urea Nitrogen:

Minor increases in blood urea nitrogen (3.8%) and serum creatinine (4.2%) were observed in patients with essential hypertension treated with lisinopril / hydrochlorothiazide. More marked increases have also been reported and were more likely to occur in patients with bilateral renal artery stenosis. (See PRECAUTIONS - Renal Impairment).

Increases in blood urea nitrogen and serum creatinine, usually reversible upon discontinuation of therapy, were observed in 1.1 and 1.6% of patients respectively with essential hypertension treated with lisinopril alone.

Serum Uric Acid, Glucose, Magnesium, Cholesterol, Triglycerides and Calcium:

(see PRECAUTIONS - Metabolism).

Hemoglobin and Hematocrit: Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.5 g percent and 1.5 vol percent, respectively) occurred frequently in hypertensive patients treated with lisinopril / hydrochlorothiazide but were rarely of clinical importance unless another cause of anemia coexisted. In clinical trials, 0.4% of patients discontinued therapy due to anemia. Rarely, hemolytic anemia has been reported.

Agranulocytosis and bone marrow depression, manifested as anemia, cytopenia or leucopenia, have been caused by angiotensin converting enzyme inhibitors, including lisinopril. Several cases of agranulocytosis and neutropenia have been reported in which a causal relationship to lisinopril cannot be excluded (see WARNINGS - Neutropenia / Agranulocytosis).

Post-marketing experience

The following undesirable effects have been observed and reported during treatment with Lisinopril/Hydrochlorothiazide with the following frequencies: Very common (= 10%), common (= 1%, < 10%), uncommon (= 0.1%, < 1%), rare (= 0.01%, < 0.1%), very rare (< 0.01%) including isolated reports.

Blood and lymphatic system disorders

Rare: anaemia

Very rare: agranulocytosis, bone marrow depression, thrombocytopenia, leucopenia, hemolytic anaemia (see WARNINGS – Neutropenia/Agranulocytosis).

Metabolism and nutrition disorders

Uncommon: gout

Rare: hyperkalaemia (see PRECAUTIONS – Hyperkalaemia), hypokalaemia hyperuricemia, hyperglycaemia (see PRECAUTION – Metabolism).

Nervous system and psychiatric disorders

Common: dizziness, headache, paraesthesia

Cardiac and vascular disorders

Common: orthostatic effects (including hypotension)

Uncommon: palpitations

Respiratory, thoracic and mediastinal disorders

Common: cough (See PRECAUTIONS – Cough)

Gastrointestinal disorders

Common: diarrhoea, nausea, vomiting.

Uncommon: dry mouth.

Rare: pancreatitis.

Very rare: intestinal angioedema.

Hepato-biliary disorders

Very rare: hepatitis-either hepatocellular or cholestatic, jaundice, hepatic failure. Very rarely, it has been reported that in some patients the undesirable development of hepatitis has progressed to hepatic failure. Patients receiving lisinopril/ hydrochlorothiazide who develop jaundice or marked elevation of hepatic enzymes should discontinue lisinopril/hydrochlorothiazide and receive appropriate medical follow up (see WARNINGS – Patients with Impaired Liver Function).

Skin and subcutaneous tissue disorders

Common: rash

Rare: hypersensitivity/angioneurotic oedema: angioneurotic oedema of the face, extremities, lips, tongue, glottis and/or larynx (see section WARNINGS – Angioedema).

A symptom complex has been reported which may include one or more of the following: fever, vasculitis, myalgia, arthralgia/arthritis, a positive antinuclear antibodies (ANA), elevated red blood cell sedimentation rate (ESR), eosinophilia and leucocytosis, rash, photosensitivity or other dermatological manifestation may occur.

Musculoskeletal, connective tissue and bone disorders

Common: muscle cramps

Rare: muscle weakness

Reproductive system and breast disorders

Common: impotence

General disorders and administration site conditions

Common: fatigue, asthenia

Uncommon: chest discomfort

Investigations

Common: increases in blood urea, increases in serum creatinine (see PRECAUTIONS – Renal Impairment) , increases in liver enzymes (see WARNINGS – Patients with Impaired Liver Function), decreases in haemoglobin.

Uncommon: decreases in haematocrit.

Rare: increases in serum bilirubin(See WARNINGS – Patients with Impaired Liver Function)

Lisinopril

Myocardial infarction or cerebrovascular accident possibly secondary to excessive hypotension in high risk patients, tachycardia, abdominal pain and ingestion, mood alterations, mental confusion and vertigo have occurred; As with other angiotensin converting enzyme inhibitors,

taste disturbance and sleep disturbance have been reported; bronchospasm, rhinitis, sinusitis, alopecia, urticaria, diapheresis, pruritis, psoriasis and severe skin disorders (including pemphigus, toxic epidermal necrolysis, Steven-Johnson Syndrome and erythema multiforme, have been reported; hyponatraemia, uraemia, oliguria/anuria, renal dysfunction, acute renal failure, pancreatitis, Rarely haemolytic anaemia has been reported.

Hydrochlorthiazide

Anorexia, gastric irritation, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis, sialoadenitis, vertigo, xanthopsia, leucopenia, agranulocytosis, thrombocytopenia, aplastic anemia, haemolytic anaemia, purpura, photosensitivity, urticaria, necrotizing angiitis (vasculitis) (cutaneaous vasculitis), fever, respiratory distress including pneumonitis and pulmonary oedema, anaphylactic reactions, hyperglycaemia, glycosuria, hyperuricemia, electrolyte imbalance including hyponatremia, muscle spasm, restlessness, transient blurred vision, renal failure, renal dysfunction and interstitial nephritis.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

No specific information is available on the treatment of overdosage with lisinopril and hydrochlorothiazide tablets. Treatment is symptomatic and supportive. Therapy with lisinopril and hydrochlorothiazide tablets should be discontinued and the patient observed closely. Suggested measures include induction of emesis and/or gastric lavage, if ingestion is recent, and correction of dehydration, electrolyte imbalance and hypotension by established procedures.

Lisinopril

Overdose symptoms include severe hypotension, electrolyte disturbances and renal failure. Overdosed patients should be kept under very close observation. Therapeutic measures depend on the nature and severity of symptoms. Measures to prevent absorption and methods to speed elimination should be employed. If severe hypotension occurs, place the patient in the shock position and infuse intravenous normal saline immediately. Vasopressors including angiotensin II may be considered if fluid replacement is inadequate or contraindicated. Circulating lisinopril may be removed by hemodialysis. Avoid high-flux polyacrylonitrile dialysis

membranes (see PRECAUTIONS - Anaphylactoid Reactions during membrane exposure). Serum electrolytes and creatinine should be monitored frequently.

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.

DOSAGE AND ADMINISTRATION

Essential Hypertension

Dosage must be individualized. The fixed combination is not for initial therapy. The dose of NU-LISINOPRIL /HCTZ (lisinopril and hydrochlorothiazide) should be determined by the titration of the individual components. NU-LISINOPRIL /HCTZ should be taken at the same time each day.

Once the patient has been successfully titrated with the individual components as described below, NU-LISINOPRIL /HCTZ 10/12.5 mg or one or two 20/12.5 mg or 20/25 mg tablets once daily may be substituted if the titrated doses are the same as those in the fixed combination. (See INDICATIONS AND CLINICAL USE and WARNINGS)

Patients usually do not require doses in excess of 50 mg of hydrochlorothiazide daily, particularly when combined with antihypertensive agents.

For lisinopril monotherapy the recommended initial dose in patients not on diuretics is 10 mg of lisinopril once a day. Dosage should be adjusted according to blood pressure response. The usual dosage range of lisinopril is 10 to 40 mg administered in a single daily dose. The antihypertensive effect may diminish toward the end of the dosing interval regardless of the administered dose, but most commonly with a dose of 10 mg daily. 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, an increase in dose should be considered. The maximum dose used in long-term controlled clinical trials was 80 mg/day.

If blood pressure is not controlled with lisinopril alone, a low dose of a diuretic may be added. Hydrochlorothiazide 12.5 mg has been shown to provide an additive effect. After the addition of a diuretic, it may be possible to reduce the dose of lisinopril.

Diuretic Treated Patients

In patients who are currently being treated with a diuretic, symptomatic hypotension occasionally may occur following the initial dose of lisinopril. The diuretic should if possible, be discontinued for two to three days before beginning therapy with lisinopril to reduce the likelihood of hypotension (see WARNINGS-Hypotension). The dosage of lisinopril should be adjusted according to blood pressure response.

If the patient's blood pressure is not controlled with lisinopril alone, diuretic therapy may be resumed as described above.

If the diuretic cannot be discontinued, an initial dose of 5 mg of lisinopril alone should be administered and the patient remain under medical supervision for at least two hours, and until blood pressure has stabilized for at least an additional hour (see WARNINGS-Hypotension and PRECAUTIONS, Drug Interactions).

Dosage Adjustment in Renal Impairment

In patients with creatinine clearance greater than 30 mL/min the usual dose titration of the individual components is required.

Anaphylactoid reactions have been reported in patients dialysed with high-flux membranes (e.g.: polyacrylonitrile [PAN] and during low density lipoproteins (LDL) apheresis with dextran sulphate and treated concomitantly with an ACE inhibitor). (See PRECAUTIONS-Anaphylactoid Reactions during membrane exposure).

For patients with creatinine clearance between 10 and 30 mL/min the starting dose of lisinopril is 2.5 - 5.0 mg/day. The dosage may then be titrated upward until blood pressure is controlled or to a maximum of 40 mg daily.

When concomitant diuretic therapy is required in patients with severe renal impairment (creatinine clearance < 10 mL/min), a loop diuretic, rather than a thiazide diuretic is preferred for

use with lisinopril. Therefore, for patients with severe renal dysfunction the lisinopril-hydrochlorothiazide combination tablet is not recommended.

AVAILABILITY OF DOSAGE FORMS

NU-LISINOPRIL /HCTZ Tablets 10/12.5 mg

Each pink, oval, unscored tablet imprinted “10" over “12.5" on one side, contains lisinopril 10 mg and hydrochlorothiazide 12.5 mg. Available in bottles of 100.

NU-LISINOPRIL /HCTZ Tablets 20/12.5 mg

Each white to off-white, oval, unscored tablet imprinted “20" over “12.5" on one side, contains lisinopril 20 mg and hydrochlorothiazide 12.5 mg. Available in bottles of 100.

NU-LISINOPRIL /HCTZ Tablets 20/25 mg

Each pink, oval, unscored tablet imprinted “20" over “25" on one side, contains lisinopril 20 mg and hydrochlorothiazide 25 mg. Available in bottles of 100.

PHARMACEUTICAL INFORMATION

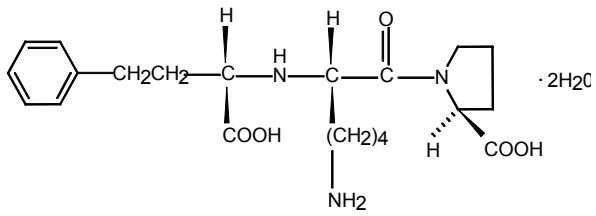
Drug Substance

Proper name: Lisinopril

Chemical name:

(S)-1-[N^2-(1-carboxy-3-phenyl-propyl)-L-lysyl]-L-proline dihydrate

Structural formula:



Molecular formula:

$C_{21}H_{31}N_3O_5.2H_2O$

Molecular weight:

441.53

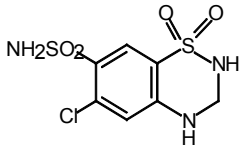
Description:

Lisinopril is a white to off-white, crystalline powder. It is soluble in water and sparingly soluble in methanol and practically insoluble in ethanol.

Proper name: Hydrochlorothiazide

Chemical name:
6-chloro-3,4-dihydro-2H-1,2,4- benzothiadiazine-7-sulfonamide 1,1-dioxide

Structural formula:



Molecular formula:
$C_7H_8ClN_3O_4S_2$

Molecular weight:
297.72

Description: Hydrochlorothiazide is a white or practically white crystalline compound with low solubility in water, but is readily soluble in dilute aqueous sodium hydroxide.

Composition

In addition to the active ingredients, lisinopril and hydrochlorothiazide, each tablet contains non-medicinal ingredients anhydrous lactose, magnesium stearate, and croscarmellose sodium. The 10/12.5 mg and 20/25 mg tablets also contain red and yellow iron oxides.

Storage

Store at controlled room temperature 15-30°C. Keep container tightly closed. Protect from light.

PHARMACOLOGY

Lisinopril Pharmacology

Study	Species/strain	Number of animals/group	Route	Dose	Results
MECHANISM OF ACTION					
In vitro ACE inhibitory activity*	Hog plasma		*In vitro*		IC_{50} = 1.7 ±0.5nM
Augmentation of contractile response to bradykinin	Guinea pig ileum	7 segments	*In vitro*		AC_{50} = 1.6nM
In vivo ACE inhibition in the rat**	Male Sprague/Dawley	8	I.V.		ID_{50} = 2.3 (1.7-3.1) µg/kg
Duration of ACE Inhibitory activity of lisinopril in rats**	Male Sprague/Dawley	4	I.V.	3 & 10 µg/kg	Duration approx. 110 min.
In vivo ACE Inhibitory activity of lisinopril in conscious rats**	Sprague/Dawley	3 - 5	P.O.	0.03-3.0 mg/kg (single dose)	Duration of at least 360 min.
In vivo ACE inhibition in anesthetized dogs**	Mongrel	6	I.V.	1-30 µg/kg	ID_{50} = 6.5 µg/kg
In vivo ACE inhibitory activity of lisinopril in conscious dogs**	Mongrel	3	P.O.	0.05-1.0 mg/kg (single dose)	Duration of action of between 6-24 hrs
EFFECTS ON BLOOD PRESSURE					
Antihypertensive activity in renal hypertensive dogs (single doses)	Mongrel	3	P.O.	0.3 mg/kg with and without hydro-chlorothiazide	After 2 hours: Lisinopril alone: 5% reduction in mean systolic pressure vs pretreatment. Lisinopril + HCTZ = 11% reduction in mean systolic pressure vs. pretreatment.
Antihypertensive activity in rats on a sodium-deficient diet (single doses)	Male Sprague/Dawley	5	P.O.	- 3.0 mg/kg daily for 4 days	After 2 hours: 11% reduction in mean systolic pressure vs pretreatment at 1 mg/kg. 22% reduction in mean systolic pressure vs. pretreatment at 3 mg/kg. Consistent response over 4 days.
Antihypertensive in 2 kidney Grollman hypertensive rats (single doses)	Male Sprague/Dawley	6 - 7	P.O.	1 & 3 mg/kg	At 2 hours: approx. 6% reduction in mean systolic pressure vs pretreatment with the antihypertensive effect lasting up to 24 hours.
Antihypertensive activity in spontaneously hypertensive rats with and without hydroclorothiazide	SH rats	3-6	P.O.	1.25 mg/kg HCTZ = 50 mg/kg daily for 3 days	Enhancement of hypotensive activity over 3 - 5 days. 2 hours after drug administration lisinopril alone reduced the average mean arterial pressure from 198 to 161 mmHg. In combination with HCTZ the average mean arterial pressure was reduced from 202 to 132 mmHg.

Antihypertensive activity in spontaneously hypertensive rats (single doses)	SH rats	36593	P.O. & I.V.	0.1 - 20 mg/kg	Slight fall in blood pressure at 0.312 - 5 mg/kg P.O. Pronounced fall at 20 mg/kg P.O. and 0.1 mg/kg I.V. with statistically significant reductions being observed for the majority of time points between ½ - 18 hours.

*Inhibition of enzymatic activity of hog plasma ACE using ^{14}C labeled substrate
**Blockage of functional (pressor) response to AI challenge.

Hydrochlorothiazide Pharmacology

Hydrochlorothiazide increases the excretion of sodium and chloride in approximately equivalent amounts 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 coadministration of probenecid without, however, an accompanying reduction in diuresis.

Lisinopril And Hydrochlorothiazide Pharmacology

In spontaneously hypertensive rats (SHR) lisinopril was studied in an oral dose of 1.25 mg/kg daily, given alone or concomitantly with hydrochlorothiazide 50 mg/kg orally, for 3 days. Reductions in blood pressure were recorded (tail cuff method) on each of the 3 treatment days, reaching normotensive levels (113-116 mmHg) on Day 3 at 4-8 hours after the concomitant therapy.

TOXICOLOGY

Lisinopril Toxicology

Acute Toxicity of Lisinopril

LD_{50} Values

Route	Species	Sex	LD_{50} (g/kg)
Oral	Mouse	Male	>20
	Mouse	Female	>20
	Rat	Male	>20
	Rat	Female	>20
	Dog	Male	> 6
	Dog	Female	> 6
Intravenous	Mouse	Male	>10
	Mouse	Female	>10
Intraperitoneal	Rat	Male	>10
	Rat	Female	>10

Signs of toxicity: Following oral administration to mice decreased activity and one male death (1/10) occurred. No signs of toxicity occurred in rats after oral administration. Dogs given 6 g/kg had transient diarrhea and increases in serum urea nitrogen. Intravenous administration to mice produced bradypnea, ataxia, clonic convulsions, exophthalmia, and tremors. After intraperitoneal administration in rats, ataxia and one female death (1/10) occurred. No signs of toxicity or death occurred in the males.

Subacute/Chronic Toxicology (lisinopril)

Species	Duration	No. of Animals/Group	Route	Dose mg/kg/day	Results
Rat	2-Week	10 F + 10 M	Oral	3,10,30	At all doses, decrease of 2 to 16% in weight gain and 12 to 14% in heart weights were observed in female rats.
Rat	3-Month with 1-Month Interim	25 F + 25 M	Oral	3,10,30	At all doses, increased serum urea nitrogen values (up to approximately 2-fold) and decreased heart weights (7 to 10%) were observed in female rats. At 10 and 30 mg respectively weight gain decreased 11 to 14% in males. An increased incidence of focal erosions of the gastric mucosa and focal renal tubular basophilia were also seen.
Rat	1-Year with 6-Month Interim	25 F + 25 M	Oral	2,5,10,30, 90[a]	At all doses, a decrease in weight gain (up to 16%) was observed. Serum urea nitrogen increased up to 4-fold; serum sodium decreased (average down to 3 mEq/L) and serum potassium increased (average up to 0.5 mEq/L). At 2, 5, 10 and 30 mg heart weight decreased; at 5, 10, and 30 mg, kidney weight increased; and at 5, 10, 30, and 90 mg, renal tubular basophilia increased. At 10, 30 and 90 mg, focal interstitial nephritis was observed.
Rat	3-Month with a 1-Month Interim and a 1-Month Recovery	30 F + 30 M	Oral	3,30,300, 3000	At all doses, weight gain decreased by 5 to 11%, and increases were observed in serum urea nitrogen (up to approximately 3-fold) and serum potassium (average up to 0.4 mEq/L). At 30, 300 and 3000 mg there was an increased incidence of focal renal tubular basophilia and focal necrosis of the glandular mucosa of the stomach. An increased incidence of focal tubular basophilia persisted in rats given 300 or 3000 mg/kg/day.
Rat	1-Month	15 F + 15 M	Oral	30,60 30, 60 (with saline)	Saline supplementation prevented decreased weight gain and elevations in serum urea nitrogen at 30 and 60 mg. Decreases in cardiac weight at 30 and 60 mg, were suppressed by saline supplementation in males at 30mg. At 30 and 60 mg renal changes produced due to a low salt diet (renal tubular degeneration and renal tubular basophilia) were prevented by saline supplementation. Mild gastric erosions or necrotic changes were seen in 1 or 2 of 30 rats given 30 or 60 mg. These gastric changes were not seen in saline supplemented animals given these doses; however, the relationship of amelioration due to saline is uncertain because of the low incidence of this change which is also occasionally seen in untreated animals.
Rat	5 Days 6 Days Recovery	8 M	Oral	5, 300	Consumption of 2% saline increased during treatment at 5 mg and on Days 2 to 4 post-treatment at 300 mg.

[a] Dosing terminated week 11, rats killed week 27.

Subacute/Chronic Toxicology (lisinopril continued)

Species	Duration	No. of Animals/Group	Route	Dose mg/kg/day	Results
Dog	2-Week	3 F + 3 M	Oral	3,10,30	At 30 mg, slight mineralization of the papilla muscle of the heart was seen in 1 of 6 dogs.
Dog	3-Month with 1-Month Interim	5 F + 5 M	Oral	3,10,30	At 10 mg hemoglobin concentration, hematocrit, and erythrocyte count decreased in 2 dogs. Marked increases in serum urea nitrogen and creatinine were observed in 2 of 10 dogs. One of these dogs had marked renal tubular degeneration and ulcers of the tongue, gums and gastric pyloric mucosa related to uremia. At 30 mg there was an increase in serum urea nitrogen (average up to 2-fold) and a decrease in serum sodium (down to 4 mEq/L) and serum chloride (down to 3 mEq/L). At 10 and 30 mg average cardiac weight decreased (13 to 15%).
Dog	1 Year with 6 Month Interim	5 F + 5 M	Oral	3,5,15	At 15 mg, increases were observed in serum urea nitrogen (less than 2-fold). Decreases in serum-sodium (average down to 2 mEq/L) and increases in serum potassium (average up to 0.5 mEq/L) occurred at all doses.
Dog	18-Day	3 F + 3 M	Oral	60,90 with and without saline	Saline supplementation prevented increases in serum urea nitrogen in dogs given 60 mg for 6 days followed by 90 mg for 8 or 9 days.
Dog	7-Day	4 F + 4 M	IV	60,90	Decreases in blood pressure and increases in serum urea nitrogen occurred in dogs given 60 or 90 mg/kg/day. Supplementation with physiologic saline (25 mL/kg one hour prior to dosing and 4 hours after dosing) prevented these changes. Increased serum potassium (average up to 0.6 mEq/L) and decreased serum chloride (average down to 0.4 mEq/L) values were seen both in both supplemented and unsupplemented animals.
Dog	1-Month	2 F + 2 M	Oral	3,30,300 and 1000	At 30 mg or greater, BUN increased and specific gravity of the urine decreased. Hyperplasia of renal epithelial cells were observed and deaths occurred. Dogs that died had dilation of distal renal tubules and fatty degeneration of renal tubular epithelium. No drug-related effects were observed at 3 mg.

Subacute/Chronic Toxicology (lisinopril continued)

Species	Duration	No. of Animals/Group	Route	Dose mg/kg/day	Results
Dog	3-Month with 1-Month Recovery (high dose)	Control 5 M + 5 F 3,10 & 30 mg/kg/day 3 M + 3 F 100 mg/kg/day 8 M + 8 F Recovery Control 2 M + 2 F 100 mg/kg/day 5 M + 5 F	Oral	3,10,30 and 100	Eight of 16 dogs given 100 mg died or were killed because of poor physical condition. One of 6 dogs given 30 mg was killed because of poor physical condition. At 10 mg or greater increased BUN and dilation of renal tubules was seen. Fatty degeneration of renal tubular epithelium occurred at the 2 highest dosage levels. The changes are reversible as only slight dilation of renal tubules was present in some animals given 100 mg after 4 weeks of recovery.
Rabbit	2 Weeks	6 F	Oral	15 (1,6 & 13 doses) with and without saline	Renal tubular basophilia and renal tubular dilation (considered sequela to necrosis) were seen after 6 and 13 doses in unsupplemented rabbits. Two supplemented rabbits (6 doses) also had the same renal lesion. One rabbit drank very little saline and had increases in BUN, creatinine, and potassium. Increases in these parameters were seen in unsupplemented animals after 1, 6 and 13 doses.

Teratology Studies (lisinopril)

Species	Duration	No. of Animals/Group	Route	Dose mg/kg/day	Results
Mice	25	100,300,1000, 1000 with saline	Oral	Day 6 through Day 15 of gestation	No teratogenic effect was observed. There was an increased incidence of resorptions in all unsupplemented groups (no increase in serum urea nitrogen).
Rat	35	30,100,300, 300 with saline	Oral	Day 6 through Day 17 of gestation	No teratogenic effect was observed. Maternal weight gain decreased in all unsupplemented groups. The open field behavioral test (measure of spontaneous activity) showed increased activity in Week 5 postpartum F1 females at 300 mg with and without saline, but only in 300 mg with saline females in Week 6. When the open field test was repeated in males and females given 300 mg with and without saline in Week 11, no increase in activity was seen.
Rabbit (New Zealand)	18	0.1, 0.3,1.0 all groups with saline	Oral	Day 6 through Day 18 of gestation	No teratogenic effect was observed. At all doses there was an increased incidence of incomplete ossification sternebrae, metacarpals, forefoot phalanges, pelvic bones and tali and/or calcanea) which was considered to represent a fetotoxic effect. At 1 mg one rabbit had a high incidence of resorptions.
Rabbit (New Zealand)	18	0.031, 0.125, 0.5	Oral	Day 6 through Day 18 of gestation	No fetotoxicity, nor embryotoxicity was observed at maternotoxic doses. At 0.125 and 0.5 mg maternal deaths, decreased maternal weight gain and food consumption, as well as increases in BUN, creatinine and potassium were seen. In addition, doses of 0.5 mg produced decreases in serum sodium and chloride, diffuse distention of the renal distal tubules and degeneration of renal tubules.

Fertility and Late Gestation and Lactation with Postnatal Evaluation Studies (lisinopril)

Species	No. of Animals/Group	Route	Dose mg/kg/day	Duration of Dosing	Results
Rat	24 F & 24 M	Oral	30,100, 300 300 with saline	Males were dosed for 78 days prior to mating and females from 15 days prior to mating until sacrifice on Day 20 of gestation.	Weight gain was reduced in unsupplemented males at all doses and during gestation in unsupplemented females. No effects on fertility and no signs of teratogenicity were observed. There was an increase in F1 pup deaths (3 to 8% vs. control 1%) Day 1 to 7 postpartum in 100 and 300 mg (saline and nonsaline) groups. Decreased mean F1 pup weight (3 to 7% less than controls) on Day 0 postpartum was seen in all unsupplemented groups.
Rat	20 F	Oral	30,100,300 300 with saline	Day 15 of gestation through Day 21 postpartum	On Days 2 to 7 postpartum there was an increased number of dead pups (8 to 10% vs. control 0%). On Day 21 postpartum, a decrease in pup weights (8% less than controls) was observed in the unsupplemented 100 and 300 mg groups. There was no effect in the supplemented group. Pup development was not altered.

Genotoxicity Studies (lisinopril)

Study	Test System	Dose	Results
Mutagenesis			
Microbial mutagen with and without metabolic activation	*Salmonella typhimurium* TA1535, TA1537, TA98, TA100	up to 2000 μg/plate	Negative for mutagenic potential.
	Escherichia coli WP2, WP2 uvrA	up to 10 mg/plate	
In vitro V-79 mammalian cell mutagenesis with and without metabolic activation	Chinese Hamster Lung Cell	up to 10 mM (4.42 mg/mL)	Negative for mutagenic potential.
DNA Damage			
In vitro alkaline elution	Rat Hepatocyte	up to 30 mM (13.25 mg/mL)	Negative for induction of DNA single strand breaks.
Chromosomal Evaluation			
In vitro chromosomal aberration assay with and without metabolic activation	Chinese Hamster Ovary	up to 30 mM (13.25 mg/mL)	Negative for induction of chromosomal aberration.
In vivo chromosomal aberration assay	Bone Marrow Cells of Male Mice	up to 5000 mg/kg	Negative for increases in chromosomal aberrations.

Carcinogenicity Studies (lisinopril)

Species	Duration	No. of Animals/Group	Route	Dose mg/kg/day	Results
Mice Cri:CD-1(ICR)BR	92 weeks	50 F & 50 M	Oral	15,45,135 mg/kg/day	No evidence of carcinogenic effect was observed. Decreased weight gain (7 to 15%) was seen in females at 135 mg. A greater incidence and severity of chronic nephritis in females and males given 45 and 135 mg was also seen.
Rats Cri:CD(SD)BR	105 weeks	50 F & 50 M	Oral	10,30,90 mg/kg/day	No evidence of carcinogenic effect was observed. Decreased weight gain (5 to 14%) in male drug-treated rats during the first 67 weeks of the study was observed. Focal sacculations of the retinal vessels was more prevalent in rats given 30 or 90 mg than in controls in Drug Week 100. An increased incidence of renal tubular hypertrophy in drug-treated males was seen at termination of the study (1 mg was considered the no-effect dose for this change in males based on an additional 105 week study at 1, 3, and 10 mg/kg/day). An increased incidence of chronic nephritis in drug-treated females (10 mg is the no-effect dose based on an additional 105 week study at 1, 3, and 10 mg/kg/day) was observed.

Hydrochlorothiazide Toxicology

Hydrochlorothiazide was found to have relatively low toxicity in acute and chronic toxicity studies. In acute animal toxicity studies in mice the LD_{50} was greater than 10,000 mg/kg suspension orally and was 884 mg/kg intravenously. In rats the acute LD_{50} was greater than 10,000 mg/kg suspension orally and 3,130 mg/kg suspension intraperitoneally. In the rabbit the acute intravenous LD_{50} 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, 1000 and 2000 mg/kg/day of suspension five days a week for three weeks displayed no sign of drug effect. Three of the rats given 2000 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 1000 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 2000 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.

Toxicology (lisinopril and hydrochlorothiazide)

Species	Duration	No. of Animals/Group	Route	Dose	Effects
Rat	2-weeks	10 M + 10 F	Oral	Lisinopril, 0,3,10, 30 mg/kg/day; Lisinopril/HCTZ* 3/10, 10/10 30/10 mg/kg/day	Decreased body weight gain was seen in all the drug-treated groups. A decrease in serum chloride occurred in all groups given the combination. Increased serum urea nitrogen occurred in the 2 highest groups given the combination. Renal tubular degeneration and gastritis or gastric ulcer occurred in one rat each at 10/10 and 30/10 mg/kg/day. An additional rat at 30/10 mg/kg/day also had a gastric ulcer without renal lesions. Decreased average heart weight (females) was seen in all the groups given the combination.
Rat	14-weeks	25 M + 25 F	Oral	Toxicity study with one month interim necropsy Lisinopril/HCTZ 0/0, 3/10, 10/10 30/10 mg/kg/day	Decreased body weight gain, increased serum urea nitrogen, decreased serum sodium and chloride, and decreased average heart weights, occurred at all dosage levels. Very slight focal necrosis of the fundic mucosa of the stomach occurred in the 2 highest dosage groups. Focal renal tubular basophilia occurred at a higher incidence in drug-treated animals compared to control animals.
Rat	27-weeks	15 M + 15 F	Oral	Lisinopril/HCTZ 0/0, 3/10, 10/10 30/10 mg/kg/day	All animals had average body weight gains approximately 5 to 25% below the controls throughout the study. Average serum nitrogen values were generally two to three times greater in drug-treated animals compared to controls. Other serum biochemical parameters changed very slightly. Decreases in erythrocyte parameters were seen at all dosage levels. Decreases in heart weight occurred at all dosage levels and increase in kidney weight occurred at the 2 highest dosage levels. Mineralization of the renal cortico-medullary junction occurred in 2 to 5 rats in each of the drug-treated groups. Very small or small necrotic foci of gastric mucosa occurred in 5 rats in the high dose group. Chronic nephritis and its early stage of renal tubular basophilia occurred among treated and control rats, but occurred at a greater incidence in treated rats.

*Hydrochlorothiazide

Toxicology (lisinopril and hydrochlorothiazide) (continued)

Species	Duration	No. of Animals/Group	Route	Dose	Effects
Dog	2-weeks	3 M + 3 F	Oral	Lisinopril, 0,3,10, 30 mg/kg/day; Lisinopril/HCTZ 3/10, 10/10 30/10 mg/kg/day	Average body weight losses in dogs given lisinopril 30 mg/kg/day or lisinopril 10 or 30 mg/kg/day with hydrochlorothiazide were probably related to treatment. Increase in serum urea nitrogen, creatinine and phosphorus occurred at the 2 highest dosage levels of the combination. At these doses renal tubular degeneration and secondary lymphoid depletion and gastrointestinal lesions were seen. At the highest dose increases in SGPT, alkaline phosphatase, potassium, and calcium and decreases in serum chloride, necrosis of hepatocytes, and mineralization of the papillary muscle of the heart were seen.
Dog	14-weeks	5 M + 5 F	Oral	Toxicity study with one month interim necropsy Lisinopril/HCTZ 0/0, 1/10, 3/10 10/10 mg/kg/day	3 dogs given 10/10 mg/kg/day of lisinopril/hydrochlorothiazide showed physical signs that were attributable to drug treatment; these included decreased activity, dehydration and anorexia. Marked increases in the serum concentrations of urea nitrogen (128.4 to 271.5 mg/100 mL), creatinine (5.1 to 11.5 mg/100 mL), and phosphorus (9.2 to >16.0 mg/100mL) in terminal samples of 3 dogs given 10/10 mg/kg/day of lisinopril/hydrochlorothiazide that were sacrificed due to their poor physical condition after 11 or 18 doses. These dogs had renal tubular necrosis and secondary lymphoid depletion, and gastrointestinal lesions. At 3/10 mg/kg/day, an increase in serum urea nitrogen was seen. At all doses decreases in serum sodium, potassium, and chloride occurred probably due to hydrochlorothiazide.
Dog	27-weeks	3 M + 3 F	Oral	Lisinopril/HCTZ 0/0, 0.3/1, 1/3, 3/10 mg/kg/day	All dogs given 3/10 mg/kg/day had elevations in serum urea nitrogen and some had increases in serum creatinine. One dog at this level was markedly affected with increases in serum urea nitrogen, creatinine, glucose, GOT, and GPT and decreases in serum sodium, chloride, and potassium. This dog was killed in the fifth week and had renal tubular degeneration and secondary lymphoid depletion and gastrointestinal lesions. A transient decrease in blood erythroid parameters were seen at the highest dosage level and a decrease in serum sodium and at necropsy males in this group had a mild hypertrophy of the renal proximal tubules probably due to hypokalemia. The only changes seen at 0.3/1 and 1/3 mg/kg/day were decreases in serum potassium and chloride, and elevation in serum urea nitrogen at 1/3 mg/kg/day.

Teratology (lisinopril and hydrochlorothiazide)

Species	Duration	No. of Animals/Group	Route	Dose	Effects
Mouse	4-weeks	25 F	Oral	Lisinopril/HCTZ 0/0, 10/10, 30/10, 90/10 mg/kg, 90/10 mg/kg + 0/9% Saline - Days 6 - 15 of Gestation	There were no maternal deaths and no treatment-related abortions. In all drug-treated groups there were no treatment-related effects on mean live fetal weights and numbers of implants and live and dead fetuses. There was a dose-response increase in incidence of skeletal malformations. In addition, there was an increase in the incidence of lumbar ribs, a skeletal-variation, among drug treated groups. All of the skeletal malformations, with the exception of the fetus with the extra vertebra, were among mice not given saline supplementation and have occurred at comparable incidences in control groups of other studies, and some were observed in the control group of this study. A repeat of this study did not produce any evidence of treatment-related fetal skeletal malformations.
Rat	4-weeks	25 F	Oral	Lisinopril/HCTZ 0/3, 10/10, 30/10, 90/10 mg/kg + 0.9% Saline - Days 6-17 of Gestation	In the lisinopril/hydrochlorothiazide 90/10 mg/kg/day group, there was a significant ($P \leq 0.05$) decrease in the number of live fetuses per pregnant female. Maternotoxicity was evident in all unsupplemented drug-treated groups. There were significant ($P \leq 0.05$) treatment-related decreases in live fetal weight in all drug-treated groups not supplemented with saline. Fetal weight in the 90/10 mg/kg/day group supplemented with saline was comparable to control. There was an increased incidence of fetuses with incompletely ossified sternebrae in the 30/10 and 90/10 mg/kg/day groups without saline supplementation which were considered to represent an embryotoxic effect. Ossification was not delayed in the 10/10 mg/kg/day group or the 90/10 mg/kg/day group supplemented with saline.
Rat	4-weeks	20 or 22 F	Oral	Lisinopril/HCTZ 0/0, 3/10, 30/10, 90/10 mg/kg + 0.9% Saline - Days 6-17 of Gestation	Fetotoxicity was apparent as treatment-related decreases in live fetal weight at all dosage levels without saline supplementation which were statistically significant ($P \leq 0.05$) in the 30/10 and 90/10 mg/kg/day groups. Results from this study confirmed those of the previous study. There was a delay in ossification, consistent with decreased live weights, at all dosage levels without saline supplementation. Maternotoxicity was evident in all unsupplemented drug-treated groups.

MUTAGENICITY (lisinopril and hydrochlorothiazide)

The results of a battery of mutagenic and chromosomal aberration studies (Ames test, mammalian cell mutagenesis assay, an *in vitro* alkaline elution test for single strand DNA breaks, an *in vitro* chromosomal aberration assay in Chinese hamster ovary cells, and *in vivo* mouse bone marrow chromosome aberration) failed to reveal a genotoxic potential for the combination of lisinopril and hydrochlorothiazide.

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