Leypril - 5

Lisinopril Tablets USP 5 mg

Exported by:
Antila Lifesciences Pvt. Ltd.
16, A-One Estate, B/H Ekta Hotel, Sarkhej,
Ahmedabad-382210, Gujarat, INDIA

Manufactured by:
Stallion Laboratories Pvt. Ltd.
C1B, 305/2, 3, 4 & 5 GIDC, Kerala (Bavla),
Dist: Ahmedabad-382220, Gujarat, INDIA

Marketed by :
LEYDON PARAGON LIMITED
50 Idowu Rufai Street, Ago Palaceway, Okota
Isolo, Lagos, Oshodi-Isolo Lagos, Nigeria.

NAFDAC REG. NO.:

Mfg. Lic. No. : G/898

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50 Idowu Rufai Street, Ago Palaceway, Okota

LEYPRIL - 5

LEYPRIL - 10

Lisinopril Tablets USP 5 mg

Each Uncoated Tablet Contains:
Lisinopril (Dihydrate) USP
Equivalent to Lisinopril 5 mg.
Excipients Q.S.
Colour: Red oxide of Iron

NAFDAC REG. NO.:

Lisinopril Tablets USP 10 mg

Each Uncoated Tablet Contains:
Lisinopril (Dihydrate) USP
Equivalent to Lisinopril 10 mg.
Excipients Q.S.

NAFDAC REG. NO.:

Therapeutic Class
Angiotensin converting enzyme (ACE) inhibitors

DESCRIPTION
Lisinopril is an oral long-acting angiotensin converting enzyme inhibitor. Lisinopril, a synthetic peptide derivative, is chemically described as (S)-l-[N2-(l-carboxy-3-phenylpropyl)-L-lysyl]-L-prolinedihydrate. Its empirical formula is C2IH31N3O5.2H2O.
Lisinopril is a white to off-white, crystalline powder, with a molecular weight of 441.53.It is soluble in water and sparingly soluble in methanol and practically insoluble in ethanol.
GAPRIL is supplied as 5 mg, 10 mg tablets in a blister pack of 28 tablets for oral administration.

CLINICAL PHARMACOLOGY
Mechanism of Action
Lisinopril inhabits Angiotensin-Converting Enzyme (ACE) in human subjects and animals. ACE is a peptidyldipeptidase that catalyzes the conversion of Angiotensin I to the vasoconstrictor substance, Angiotensin II. Angiotensin II also stimulates aldosterone secretion by the adrenal cortex. The beneficial effects of lisinopril in hypertension and heart failure appear to result primarily from suppression of the renin-angiotensin-aldosterone system. Inhibition of ACE results in decreased plasma Angiotensin II which leads to decreased vasopressor activity and to decrease aldosterone secretion.

The latter decrease may result in a small increase of serum potassium. In hypertensive patients with normal renal function treated with Lisinopril alone for up to 24 weeks, the mean increase in serum potassium was approximately 0.1 mEq/L; however, approximately 15% of patients had increase greater than 0.5 mEq/L and approximately 6% had a decrease greater than 0.5 mEq/L.
In the same study, patients treated with Lisinopril and hydrochlorothiazide for up to 24 weeks had a mean decrease in serum potassium of 0.1 mEq/L; approximately 4% of patients had increases greater than 0.5 mEq/L and approximately 12% had a decrease greater than 0.5 mEq/L. (see PRECAUTIONS.)
Removal of Angiotensin II negative feedback on renin secretion leads to increased plasma renin activity.
ACE is identical to kininase, an enzyme that degrades bradykinin. Whether increased levels of bradykinin, a potent vasodepressor peptide, play a role in the therapeutic effects of Lisinopril remains to be elucidated.
While the mechanism through which Lisinopril lower blood pressure is believed to be primarily suppression of the renin¬-angiotensin-aldosterone system, Lisinopril is antihypertensive even in patients with low-renin hypertension. Although Lisinopril was antihypertensive in all races studied, Black hypertensive patients (usually a low-renin hypertensive population) had a smaller average response to monotherapy than non-Black patients.
Concomitant administration of Lisinopril and hydrochlorothiazide further reduced blood pressure in Block and non-Block patients and any racial differences in blood pressure response were no longer evident.

Pharmacokinetics and Metabolism
Adult Patients: Following oral administration of Lisinopril, peak serum concentrations of Lisinopril occur within about 7 hours, although there was a trend to a small delay in time taken to reach peak serum concentrations in acute myocardial infarction patients. 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 appear to be bound to other serum proteins. Lisinopril does not undergo metabolism and is excreted unchanged entirely in the urine. Based on urinal recovery, the mean extent of absorption of lisinopril is approximately 25%, with large inter-subject variability (6%-60%) at all doses tested (5-80mg). Lisinopril absorption is not influenced by the presence of food in the gastrointestinal tract.
The absolute bioavailability of lisinopril is reduced to 16% in patients with stable NYHA Class II-IV congestive heart failure, and the volume of distribution appears to be slightly smaller than that in normal subjects. The oral bioavailability of lisinopril in patients with acute myocardial infarction is similar to that in health volunteers.Upon multiple dosing, lisinopril exhibits an effective half-life of accumulation of 12 hours.
Impaired renal function decreases elimination of lisinopril which is excreted principally through the kidneys, but this decrease becomes clinically important only when the glomerular filtration rate is below 30 mL/min., above this glomerular filtration rate, the elimination half-life is little changed. With greater impairment, however, peak and trough lisinopril level increase, time to peak concentration increases and time to attain steady state is prolonged. Older patients, on average, have (approximately doubled) higher blood levels and area under the plasma concentration time curve (AUC) than younger patients. (See DOSAGE AND ADMINISTRATION.)Lisinopril can be removed by hemodialysis.
Studies in rats indicate that lisinopril crosses the blood-brain barrier poorly. Multiple doses of lisinopril in rats do not result in accumulation in any tissues. Milk of lactating rats contains radioactivity following administration of 14C lisinopril. By whole body autoradiography, radioactivity was found in the placenta following administration of labeled drug to pregnant rats, but none was found in the foetuses.
Pediatric Patients: The Pharmacokinetics of lisinopril was studied in 29 pediatric hypertensive patients between 6 years and 16 years with glomerular filtration rate >30 mL/min/1.73 m2. After doses of 0.1 to 0.2 mg/kg, steady state peak plasma concentrations lisinopril occurred within 6 hours and the extent of absorption based on urinary recovery was about 28%. These values are similar to those obtained previously in adults. The typical value of lisinopril oral clearance (systemic clearance/absolute bioavailability) in a child weighing 30 kg is 10 L/h, which increases in proportion to renal function.

Pharmacodynamics and Clinical Effects
Hypertension
Adult Patients:Administration of Lisinopril to patients with hypertension results in a reduction of both supine and standing blood pressure to about the same extent with no compensatory tachycardia. Symptomatic postural hypotension is usually not observed although it can occur and should be anticipated in volume and/or salt-depleted patients. (See WARNINGS.)
When given together with thiazide-type diuretics, the blood pressure lowering effects of the two drugs are approximately additive.
In most patients studied, onset of antihypertensive activity was seen at one hour after oral administration of an individual dose of Lisinopril, 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.
In some patients achievement of optimal blood pressure reduction may require two to four week of therapy.
The antihypertensive effects of Lisinopril are maintained during long-term therapy. Abrupt withdrawal of Lisinopril has not been associated with a rapid increase in blood pressure, or a significant increase in blood pressure compared to pre-treatment levels.

Two dose-response studies utilizing a once-daily regimen were conducted in 438 mild to moderate hypertensive patients not on a diuretic. Blood pressure was measured 24 hours after dosing.
An antihypertensive effect of Lisinopril was seen with 5 mg in some patients. However, in both studies blood pressure reduction occurred sooner and was greater in patients treated with 10, 20 or 80 mg of Lisinopril. In controlled clinical studies, Lisinopril 20-80 mg has been compared in patients with mild to moderate hypertension to hydrochlorothiazide 12.5-50 mg and with atenolol 50-200 mg; and in patients with moderate to severe hypertension to metoprolol 100-200 mg. It was superior to hydrochlorothiazide in effects on systolic and diastolic pressure in a population that was 3/4 Caucasian. Lisinopril was approximately equivalent to atenolol and metoprolol in effects on diastolic blood pressure, and had somewhat greater effects on systolic on systolic blood pressure.
Lisinopril had similar effectiveness and adverse effects in younger and older (>65 years) patients. It was less effective in Blacks than in Caucasians.
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 are not large.
In patients with renovascular hypertension Lisinopril has been shown to be well tolerated and effective in controlling blood pressure. (See PRECAUTIONS.)

Pediatric Patients: In a clinical study involving 115 hypertensive pediatric patients 6 to 16 years of age, patients who weighed <50 kg received either 0.625, 2.5 or 20 mg of lisinopril daily and patients who weighed ε 50 kg received either 1.25, 5 or 40 mg of lisinopril daily. At the end of 2 weeks, lisinopril administered once daily lowered trough blood pressure in a dose-dependent manner with consistent antihypertensive efficacy demonstrated at dose >1.25 mg (0.02 mg/kg).This effect was confirmed in a withdrawal phase, where the diastolic pressure rose by about 9 mmHg more in patients randomized to placebo than it did in patients who were randomized to remain on the middle and high doses of lisinopril. The dose-dependent antihypertensive effect of lisinopril was consistent across several demographic subgroups: age, Tanner stage, gender, and race. In this study, lisinopril was generally well tolerated.
In the above pediatric studies, lisinopril was given either as tablets or in a suspension for those children and infants who were unable to swallow tablets or who required a lower dose than is available in tablet in available in tablets from (see PRECAUTIONS.)

DOSAGE AND ADMINISTRATION
Heart Failure: During baseline-controlled clinical trials, in patients receiving digitalis and diuretics, single dose of Lisinopril resulted in decreases in pulmonary capillary wedge pressure, systemic vascular resistance and blood pressure accompanied by an increase in cardiac output and no change in heart rate.
In two placebo controlled, 12-week clinical studies using doses of Lisinopril up to 20 mg, Lisinopril as adjunctive therapy to digitalis and diuretics improved the following signs and symptoms due to congestive heart failure; oedema, rales, paroxysmal nocturnal dyspnoea and jugular venous distension.
In one of the studies, beneficial response was also noted for; orthopnoea, presence of third heart sound and the number of patients classified as NYHA Class III and IV. Exercise tolerance was also improved in the study. The once-daily dosing for the treatment of congestive heart failure was the only dosage regimen used during clinical trial development and was determined by the measurement of hemodynamic response. A large (over 3000 patients) survival study, the ATLAS Trial, comparing 2.5 and 35 mg of lisinopril in patients with heart failure, showed that the higher dose of lisinopril had outcomes at least as favourable as the lower dose.

Indications and Usage
Hypertension
Lisinopril is indicated for the treatment of hypertension. It may be used alone as initial therapy or concomitantly with other classes of antihypertensive agents.

Heart Failure
Lisinopril is indicated as adjunctive therapy in the management of heart failure in patients who are not responding adequately to diuretics and digitals.

Acute Myocardial Infarction
Lisinoprilis indicated for the treatment of hemodynamically stable patients within 24 hours or acute myocardial infarction, to improve survival. Patients should receive, as appropriate, the standard recommended treatments such as thrombolytic, aspirin and beta blockers.
In using Lisinopril, consideration should be given to the fact that another angiotensin-converting enzyme inhibitor, captopril, has caused agranulocytosis, particularly in patients with renal impairment or collagen vascular disease, and that available data are insufficient to show that Lisinopril does not have a similar risk. (See WARNINGS.)

In considering the use of Lisinopril should be noted that in controlled clinical trials ACE inhibitors have an effect on blood pressure that is less in Black patients than in non-Blacks. In addition, ACE inhibitors have been associated with a higher rate of angioedema in Black than in non-Black patients (see WARNINGS, Anaphylactoid and Possibly Related Reactions).

Contra-Indications
Lisinopril is contraindicated in patients who are hypersensitive to this product and in patients with a history of angioedema related to previous treatment with an angiotensin converting enzyme inhibitor and in patients with hereditary or idiopathic angioedema.

Warnings
Anaphylactoid and Possibly Related Reactions:
Presumably because angiotensin-converting enzyme inhibitors affect the metabolism of eicosanoids and polypeptides, including endogenous bradykinin, patients receiving ACE inhibitors (including Lisinopril) may be subject to a variety of adverse reactions, some of them serious.

Head and Neck Angioedema:
Angioedema of the face, extremities, lips, tongue, glottis and/or, larynx has been reported in patients treated with angiotensin converting enzyme inhibitors, including Lisinopril. This may occur at any time during treatment. ACE inhibitors have been associated with a higher rate of angioedema in Black than in non-Black patients.Lisinopril should be promptly discontinued and appropriate therapy and monitoring should be provided until complete and sustained resolution of signs and symptoms has occurred. Even in those instances where swelling of only the tongue is involved, without respiratory distress, patients may require prolonged observation since treatment with antihistamines and corticosteroids may not be sufficient. Very rarely, fatalities have been reported due to angioedema with laryngeal edema or tongue edema. Patients with involvement of the tongue, glottis or larynx are likely to experience airway obstruction, especially those with a history of airway surgery. **Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL) and/or measures necessary to ensure a patient airway should be promptly provided. (See ADVERSE REACTIONS.)**

Intestinal angioedema:
Intestinal angioedema has been reported in patients treated with ACE inhibitions. These patients presented with abdominal pain (with or-without nausea or vomiting); in some cases there was no prior history of facial angioedema and C-1 esterase levels were normal. The angioedema was diagnosed by procedures including abdominal CT scan or ultrasound, or at surgery, and symptoms resolved after stopping the ACE inhibitor.
Intestinal angioedema should be included in the differential diagnosis of patients on ACE inhibitors presenting with animal pain. Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see also INDICATIONS AND USAGE and CONTRAINDICATIONS).

Anaphylactoid Reactions during Desensitization:
Two patients undergoing desensitizing treatment with hymenoptera venom while receiving ACE inhibitors sustained life threatening anaphylactoid reactions. In the same patients, these reactions were avoided when ACE inhibitors were temporarily withheld, but they reappeared upon inadvertent re-challenge.

Anaphylactoid Reaction during Membrane Exposure:
Sudden and potentially life threatening Anaphylactoid reactions have been reported in some patients dialyzed with high-flux membranes (e.g., AN69®*) and treated concomitantly with an ACE inhibitor. In such patients, dialysis must be stopped immediately and aggressive therapy for anaphylactoid reactions is initiated, Symptoms have not been relieved by antihistamines in these situations.In these patients, consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agent. Anaphylactoid reactions have also been reported in patients undergoing low-density lipoprotein apheresis with dextran sulfate absorption

Hypotension
Excessive hypotension is rare in patients with uncomplicated treated with GAPRIL alone.Patients with heart failure given GAPRIL commonly have some reduction in blood pressure, with peak blood pressure reduction occurring 6 to 8 hours post dose. Evidence from the two-dose ATLAS trial suggested that incidence or hypotension may increase with dose of lisinopril in heart failure patients. Discontinuation of therapy because of continuing symptomatic hypotension usually is not necessary when dosing instructions are followed; caution should be observed when initiating therapy. (Sec DOSAGE AND ADMINISTRATION.)
Patients at risk of excessive hypotension, sometimes associated with oliguria and/or progressive azotemia, and rarely with acute renal failure and/or death, include those with the following conditions or characteristics: heart failure with systolic blood pressure below 100 mmHg, hyponatraemia, high dose diuretic therapy, recent intensive diuresis or increase in diuretic dose, renal dialysis, or severe volume and/or salt depletion of any etiology. It may be advisable to eliminate the diuretic (except in patients with heart failure), reduce the diuretic dose or increase salt intake cautiously before initiating therapy with GAPRIL in patients at risk for excessive hypotension who are able to tolerate such adjustments. (See PRECAUTIONS, Drug Interaction and ADVERSE REACTIONS.)
Patients with acute myocardial infarction in the GISSI-3 trial had a higher (9.0% verses 3.7%) incidence of persistent hypotension (systolic blood pressure<90 mmHg for more than 1 hour) when treated with GAPRIL. Treatment with GAPRIL must not be initiated in acute myocardial infarction patients at risk of further serious hemodynamic deterioration after treatment with a vasodilator (e.g. systolic blood pressure of 1000 mmHg or lower) or cardiogenic shock. In patients at risk of excessive hypotension, therapy should be started under very close medical supervision and GAPRIL, such patients should he followed closely for the first two weeks of treatment and whenever the dose of GAPRIL and/or diuretic is increased. Similar considerations may apply to patients with ischemic heart or cerebrovascular disease, or in patients with acute myocardial infarction, in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.
If excessive hypotension occurs, the patient should be placed in the supine position and, if necessary , receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses of GAPRIL which usually can be given without difficulty once the blood pressure his stabilized. If symptomatic hypotension develops, a dose reduction or discontinuation of GAPRIL or concomitant diuretic may be necessary.

Leukopenia/Neutropenia/Agranulocytosis
Another angiotensin converting enzyme inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients but more frequently in patients with renal impairment especially if they also have a collagen vascular disease. Available data from clinical trials of GAPRIL are insufficient to show that GAPRIL does not cause agranulocytosis at similar rate.
Marketing experience has revealed rare cause of leukopenia/neutropenia and bone marrow depression in which a causal relationship to lisinopril cannot be excluded. Periodic monitoring of white blood cell counts in patients with collagen vascular disease and renal disease should be considered.

Hepatic Failure
Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice or hepatitis and progresses to fulminant hepatic necrosis and (sometime) death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up.

Fetal/Neonatal Morbidity and Mortality
ACE inhibitor can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature. When pregnancy is detected, ACE inhibitors 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; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation and patient ductusarteriosus have also been reported, although it is not clear whether these occurrences were due to the ACE-inhibitor exposure.

These adverse effects do not appear to have resulted from intrauterine ACE-ini1bitor exposure that has been limited to the first trimester. Mothers whose embryos and foetuses are exposed to ACE inhibitors only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should make every effect to discontinue the use of GAPRIL as soon as possible.
Rarely (probably less often than once in every thousand pregnancies), no alternative to ACE inhibitors will be found.In these rare cases, the mother should be apprised of the potential hazards to their foetuses, and serial ultrasound examinations should be performed to assess the intra-amniotic environment.
If oligohydramnios is observed, GAPRIL should be discontinued unless it is considered lifesaving for the mother.Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.
Infants with histories 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 means of reversing hypotension and/or substituting for disordered renal function.Lisinopril, which crosses the placenta, has been removed from neonatal circulation by peritoneal dialysis with some clinical benefit, and theoretically may be removed by exchange transfusion, although there is no experience with the latter procedure.
No teratogenic effects of lisinopril were seen in studies of pregnant rats, mice, and rabbits. On a mg/kg basic, the doses used were upto 625 times (in mice), 188 times (in rats), and 0.6 times (in rabbits) the maximum recommended human dose.

PRECAUTIONS
General
Aortic Stenosis/Hypertrophic Cardiomyopathy:
As with all vasodilators, lisinopril should be given with caution to patients with obstruction in the outflow tract of the left ventricle.

Impaired Renal Function:
As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated insusceptible individuals. In patients with severe congestive heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin converting enzyme inhibitors, including Lisinopril may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death.
In hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine may occur. Experience with another angiotensin-converting enzyme inhibitor suggests that these increases are usually reversible upon discontinuation of Lisinopril and/or diuretic therapy. In such patients, renal function should be monitored during the first few weeks of therapy.
Some patients with hypertension or heart failure with no apparent pre-existing renal vascular disease have developed increases in blood urea nitrogen and serum creatinine, usually minor and transient, especially when Lisinopril has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction and/or discontinuation of the diuretic and/or Lisinopril may be required.
Evaluation of patients with hypertension, heart failure, or myocardial Infarction should always include assessment of renal function.

Hyperkalemia:
In clinical trials hyperkalemia (serum potassium greater than 5.7 mEq/L) occurred in approximately 2.2% of hypertensive patients and 4.8% of patients with heart failure. In most cases these were isolated values which resolved despite continued therapy. Hyperkalemia was a cause of discontinuation of therapy in approximately 0.1 % of hypertensive patients; 0.6% of patient with heart failure and 0.1 % of patients with myocardial infarction. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium sparing diuretics, potassium sparing diurectics supplement and/or potassium containing; salt substitutes, which should be used cautiously, if at all, with Lisinopril.

Cough:
Resumably due to the inhibition of the degradation of endogenous bradykinin, persistent nonproductive cough has been reported with all ACE inhibitors, almost always resolving after discontinuation of therapy. ACE inhibitor induced cough should be considered in the differential diagnosis of cough.

Surgery/Anesthesia:
In patients undergoing major surgery or during anesthesia with agents that produce hypotension, Lisinopril may block 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.

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. If it is necessary to continue the diuretic, intiate therapy with Lisinopril at a dose of 5 mg daily, and provide close medical supervision after the initial dose until blood pressure has stabilized.
When a diuretic is added to the therapy of a patient receiving Lisinopril, an additional antihypertensive effect is usually observed. Studies with ACE inhibitors in combination with diuretics indicate that the dose of the ACE inhibitor can be reduced when it is given with diuretic.

Non-steroidal Anti-Inflammatory Agents: In some patients with comprised renal function who are being treated with non-steroidal anti-inflammatory drugs, the co-administration of lisinopril may result in further deterioration of renal function. These effects are usually reversible. In a study in 36 patients with mild to moderate hypertension where the antihypertensive effects of Lisinopril alone were compared to Lisinopril given concomitantly with indomethacin, the use of indomethacin was associated with a reduced effect, although the difference between the two regimens was not significant.

Other Agents: Lisinopril has been used concomitantly with nitrates and/or digoxin without evidence of clinically significant adverse interactions. This included post myocardial infarction patients who were receiving intravenous or transdermal nitroglycerin. No clinically important pharmacokinetic interactions occurred when Lisinopril was used concomitantly with propranolol or hydrochlorothiazide. The presence of food in the stomach does not alter the bioavailability of Lisinopril.

Agents increasing Serum Potassium: Lisinopril attenuates potassium loss caused by thiazide-type diuretics. Use of lisinopril with potassium-sparing diuretics (e.g., spironolactone, triamterene or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Therefore, if concomitant use of these agents is indicated because of demonstrated hypokalemia, they should be used with caution and with frequent monitoring of serum potassium. Potassium sparing agents should generally not be used in patients with bean failure who are receiving Lisinopril.

Lithium: Lithium toxicity has been reported in patients receiving lithium concomitantly with drugs which cause elimination of sodium, including ACE inhibitors. Lithium toxicity was usually reversible upon discontinuation of lithium and the ACE inhibitor. It is recommended that serum lithium levels be monitored frequently if Lisinopril is administered concomitantly with lithium

Carcinogenesis, Mutagenesis, impairment of Fertility
There was no evidence of a tumorigenic effect when lisinopril will administered for 105 weeks to male and female rats at doses up to 90 mg/kg/day (about 56 or 9 time* the maximum recommended daily human dose, based on body weight and body surface area, respectively). There was no evidence of carcinogenicity when lisinopril was administered for 92 weeks to (male and female) mice at doses up to 135 mg/kg/day (about 84 times* the maximum recommended daily human dose). This dose was 6.8 times the maximum human dose based on body surface area in mice.
*Calculations assume a human weight of 50 kg and human body surface area of 1.62 m2.
Lisinopril was not mutagenic in the Ames microbial mutagen test with or without metabolic activation. It was also negative in a forward mutation assay using Chinese hamster lung cells. Lisinopril did not produce single strand DNA breaks in an in vitro alkaline elution rat hepatocytes assay. In addition, lisinopril did not produce increases in chromosomal aberrations in an in vitro test in Chinese hamster ovary cells or in an in vivo study in mouse bone marrow.
There were no adverse effects on reproductive performance in male and female rats treated with up to 300 mg/kg/day of lisinopril. This dose is 188 times and 30 times the maximum human dose when based on mg/kg and mg/m2, respectively.

Pregnancy
Pregnancy Categories C, (first trimester), and D (second and third trimesters). See WARNINGS, Fetal/Neonatal Morbidity and Mortality

Nursing Mothers
Milk of lactating rats contains radioactivity following administration of 14C lisinopril. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from ACE inhibitis, a decision should be made whether to discontinue nursing or discontinue Lisinopril, taking into account the importance of the drug to the mother.

Pediatric Use
Antihypertensive effects of Lisinopril have been established in hypertensive pediatric patients aged 6 to 16 years.
There are no data on the effect of Lisinopril on blood pressure in pediatric patients under the age 6 or in pediatric patients with glomerular filtration rate <30 ml/min/1.73 m2.

Geriatric Use
Clinical studies of Lisinopril in patients with hypertension did not include sufficient numbers of subject, aged 65 and over to determine whether they respond differently from younger subjects. Other clinical experience in this population has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.
In a clinical study of GAPRIL in patient with myocardial infarction, 65 years and over, no overall differences in safety or effectiveness were observed between elderly and younger patients, and other reported clinical experiences has not identified differences in responses between the elderly and younger patients. Other reported clinical experience has not identified differences in responses between elderly and younger patients, but greater sensitivity of some older individual cannot be ruled out.
Pharmacokinetic studies indicate that maximum blood levels and area under the plasma concentration time curve (AUC) are doubled in older patients (see CLINICAL PHARMACOLOGY Pharmacokinetics and Metabolism). This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function.
Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection. Evaluation of patients with hypertension, congestive heart failure, or myocardial infarction should always include assessment of renal function (see DOSAGE AND ADMINISTRATION).

Adverse Effects
Lisinopril has been found to be generally well tolerated in controlled clinical trials involving 1969 patients with hypertension or heart failure For the most part, adverse experiences were mild and transient.

Hypertension
In clinical trials in patients with hypertension treated with Lisinopril, discontinuation of therapy due to clinical adverse experiences occurred in 5.7% of patients. The overall frequency of adverse experience could not be related to total daily dosage within the recommended therapeutic dosage range. For adverse experiences occurring in greater than 1% of patients with hypertension treated with Lisinopril in controlled clinical trials, and more frequently then placebo.

Body as a Whole
Fatigue 2.5 (0.3) 4.0 (0.5) 1.0 (0.0)
Asthenia 1.3 (0.5) 2.1 (0.2) 1.0 (0.0)
Orthostatic Effects 1.2 (0.0) 3.5 (0.2) 1.0 (0.0)

Cardiovascular
Hypotension 1.2 (0.5) 1.6 (0.5) 0.5 (0.5)

Digestive
Diarrhea 2.7 (0.2) 2.7 (0.3) 2.4 (0.0)
Nausea 2.0 (0.4) 2.5 (0.2) 2.4 (0.0)
Vomiting 1.1 (0.2) 1.4 (0.1) 0.5 (0.0)
Dyspepsia 0.9 (0.0) 1.9 (0.0) 0.0 (0.0)

Musculoskeletal
Muscle Cramps 0.5 (0.0) 2.9 (0 8) 0.5 (0.0)

Nervous/Psychiatric
Headache 5.7 (0.2) 4.5 (0.5) 1.9 (0.0)
Dizziness 5.4 (0.4) 9.2 (1.0) 1.9(0.0)
Paresthesia 0.8 (0.1) 2.1 (0.2) 0.0 (0.0)
Decreased Libido 0.4 (0.1) 1.3 (0.1) 0.0 (0.0)
Vertigo 0.2 (0.1) 1.1 (0.2) 0.0 (0.0)

Respiratory : Cough 3.5 (0.7) 4.6 (0 8) 1.0 (0.0)

Upper Respiratory
Infections 2.1 (0.1) 2.7 (0.1) 0.0 (0.0)
Common Cold 1.1 (0.1) 1.3 (0.1) 0.0 (0.0)
Nasal Congestion 0.4 (0.1) 1.3 (0.1) 0.0 (0.0)
Influenza 0.3 (0.1) 1.1 (0.1) 0.0 (0.0)

Skin : Rash 1.3 (0.4) 1.6 (0.2) 0.5 (0.5)

Urogenital
Impotence 1.0 (0.4) 1.6 (0.5) 0.0 (0.0)
Chest pain and back pain were also seen, but were more common on placebo than Lisinopril.

Heart Failure
In patients with heart failure treated with Lisinopril for up to four years, discontinuation of therapy due to clinical adverse experiences occurred in 11.0% of patients. In controlled studies in patients with heart failure, therapy was discontinued in 8.1% of patients treated with Lisinopril for 12 weeks, compared to 7.7% of patients treated with placebo for 12 weeks.
The following table lists those adverse experiences which occurred in greater than 1% of patients with heart failure treated with Lisinopril or placebo for up to 12 weeks in controlled clinical trials, and more frequently on Lisinopril than placebo.

Controlled Trials

Lisinopril (n=407) Incidence (discontinuation) 12 weeks	Placebo (n=155) Incidence (discontinuation) 12 weeks

Body as a Whole
Chest Pain 3.4 (0.2) 1.3 (0.0)
Abdominal Pain 2.2 (0.7) 1.9 (0.0)

Cardiovascular
Hypotension 4.4 (1.7) 0.6 (0.6)

Digestive
Diarrhea 3.7 (0.5) 1.9 (0.0)
Nervous/Psychiatric
Dizziness 11.8 (1.2) 4.5 (1.3)
Headache 4.4 (0.2) 3.9 (0.0)

Respiratory
Upper Respiratory
Infection 1.5 (0.0) 1.3 (0.0)

Skin
Rash 1.7 (0.5) 0.6 (0.6)

Also observed at >1% with Lisinopril but more frequent or as frequent on placebo than Lisinopril in controlled trials were asthenia, angina pectoris, nausea, dyspnea, cough, and pruritus.
Worsening of been failure, anorexia, increased salivation, muscle cramps, back pain, myalgia, depression, chest sound abnormalities, and pulmonary edema were also seen in controlled clinical trials, but were more common on placebo than Lisinopril.
In the two-dose ATLAS trial in heart failure patents, withdrawals due to adverse events were not different between the low and high groups, either in total number of discontinuation (17-18%) or in rare specific events (The following adverse events, mostly related to ACE inhibition, were reported more commonly in the high dose group:

Events	% of patients High Dose (N=1568)	Low dose (N=1596)
Dizziness	18.9	12.7
Hypotension	10.8	6.7
Creatinine increased	9.9	7.0
Hyperkalemia	6.4	3.5
NPN* increased	9.2	6.5
Syncope	7.0	5.1

*NPN=non-protein nitrogen

Acute Myocardial Infarction
In the GISSI-3 trial, in patients treated with Lisinopril for six weeks following acute myocardial infarction, discontinuation of therapy occurred in 17 .6% of patients.
Patents treated with Lisinopril had a significantly higher incidence of hypotension and renal dysfunction compared with patients not taking Lisinopril.
In the GISSI-3 trial, hypotension (9.7%), renal dysfunction (2.0%), cough (0.5%), post infarction angina (0.3%), skin rush and generalized edema (0.01%), and angioedema (0.01 %) resulted in withdrawal of treatment. In elderly patients treated with Lisinopril, discontinuation due to renal dysfunction was 4.2%.
Other clinical adverse experiences occurring in 1.0% of patients with hypertension or heart failure treated Lisinopril in controlled clinical trials and rare, serious, possibly drug-related events reported in uncontrolled studies or marketing experience are listed below, and within each category are in order of decreasing severity:

Body as a Whole: Anaphylactoid reactions (see WARNINGS. Anaphylactoid and Possibly Related Reactions), syncope, orthostatic effects, chest discomfort, pain, pelvic pain, flank pain, edema, facial edema, virus infection, fever, chills, malaise.

Cardiovascular: Cardiac arrest; myocardial infarction or cerebrovascular accident possibly secondary to excessive hypotension in high risk patients (see WARNING, Hypotension); pulmonary embolism and infarction, arrhythmias (including ventricular tachycardia, atrial fibrillation, bradycardia and premature ventricular contractions), palpitations, transient ischemic attacks, paroxysmal nocturnal dyspnea, orthostatic hypotension, decreased blood pressure, peripheral edema, vasculitis.

Digestive: Pancreatitis hepatitis (hepatocellular or cholestatic Jaundice) (see WARNINGS, Hepatic Failure), vomiting, gastritis, dyspepsia, heartburn, gastrointestinal cramps, constipation, flatulence, dry mouth.

Hematologic: Rare cases of bone marrow depression, hemolytic anemia, leukopenia/neutropenia andthrombocytopenia.

Endocrine: Diabetes mellitus.

Metabolic: Weight loss, dehydration, fluid overload, gout, weight gain.

Musculoskeletal: Arthritis, arthralgia, neck pain, hip pain, low back pain, Joint pain, leg pain, knee pain, shoulder pain, arm pain, lumbago.

Nervous System/Psychiatric: Stroke, ataxia, memory impairment, tremor, peripheral neuropathy (e.g., dysesthesia), spasm, paresthesia, confusion, insomnia, somnolence, hypersomnia, irritability and nervousness.

Respiratory System: Malignant lung neoplasms, hemoptysis, pulmonary infiltrate, bronchospasm, asthma, pleural effusion, pneumonia, eosinophilic pneumonitis, bronchitis, wheezing, orthopnea, painful respiration, epistaxis, laryngitis, sinusitis, pharyngeal pain, pharyngitis, rhinitis, rhinorrhea.

Skin: Urticaria, alopecia, herpes, zoster, photosensitivity, skin lesions, skin infections, pemphigus, erythema, flushing, diaphoresis. Other severe skin reactions have reported rarely, including toxic epidermal necrolysis and Stevens-Johnson syndrome; causal relationship has not been established.

Special Senses: Visual loss, diplopia, blurred vision, tinnitus, photophobia, taste disturbances.

Urogenital System: Acute renal failure, oliguria, anuria, uremia, progressive azotemia, renal dysfunction, pyelonephritis, dysuria, urinary tract infection, breast pain.

Miscellaneous: A symptom complex has been reported which may include a positive ANA, an elevated erythrocyte sedimentation rate, arthralgia/arthritis, myalgia, fever, vasculitis, eosinophilia and leukocytosis. Rash, photosensitivity or other dermatological manifestations may occur alone or in combination with these symptoms.

Angioedema: Angioedema has been reported in patients receiving Lisinopril (0 1%) with an in higher in Black than in non-Black patients. Angioedema with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis and/or larynx occurs, treatment with Lisinopril should be discontinued and appropriate therapy instituted immediately.
In rare cases, intestinal angioedema has been reported in post marketing experience.

Hypotension: In hypertensive patients, hypotension occurred in 1.2% and syncope occurred in 0.1% of patents with an incidence higher in Black than in non-Black patients.
Hypotension or syncope was a cause of discontinuation of therapy in 0.5% of hypertensive patients. In patient, with heart failure, hypotension occurred m 5.3% and syncope occurred in 1.8% of patients. These adverse experiences were possibly dose-related and caused discontinuation of therapy in 1.8% of these patients, in the symptomatic trials. In patients treated with Lisinopril for six weeks after acute myocardial infarction, hypotension (systolic blood pressure δ100 mmHg) resulted in discontinuation of therapy in 9.7% of the patients.

Fetal/Neonatal Morbidity and Mortality: See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

Cough: See PRECAUTIONS Cough

Pediatric Patients: No relevant differences between the adverse experience profile for pediatric patients and that previously reported for adult patients were identified.
Clinical Laboratory Findings

Serum Electrolytes: Hyperkalemia (See PRECAUTIONS), hyponatremia.

Creatinine, Blood Urea Nitrogen: Minor increases in blood urea nitrogen and serum creatinine, reversible upon discontinuation of therapy, were observed in about 2.0% of patients with essential hypertension treated with Lisinopril alone. Increases were more common in patients receiving concomitant diuretics and in patients with renal artery stenosis. Reversible minor increases in blood urea nitrogen and serum creatinine were observed in approximately 11.6%, of patients with heart failure on concomitant diuretic therapy. Frequently, these abnormalities resolved when the dosage of the diuretic was decreased.

Hemoglobin and Hematocrit: Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.4 g% and 1.3 Vol %, respectively) occurred frequently in patients treated with GAPRIL but were rarely of clinical importance in patients without some other cause of anemia. In clinical trials, less than 0.1% of patients discontinued therapy due to anemia. Hemolytic anemia has been reported; a causal relationship to lisinopril cannot be excluded.

Liver Function Tests: Rarely, elevations of liver enzymes and/or serum bilirubin have occurred. Hepatic failure.)
In hypertensive patients, 2.0% discontinued therapy due to laboratory adverse experiences, principally elevations in blood urea nitrogen (0.6%), serum creatinine (0.5%) and serum potassium (0.4%).
In the heart failure trials, 3.4% of patients discontinued therapy due to laboratory adverse experiences; 1.8% due to elevations in blood urea nitrogen and/or creatinine and 0.6% due to elevations in serum potassium.
In the myocardial infarction trial, 2.0% of patients receiving Lisinopril discontinued therapy due to renal dysfunction (increasing creatinine concentration to over 3 mg/dL or a doubling or more of the baseline serum creatinine concentration); less than 1.0% of patients discontinued therapy due to other laboratory adverse experience: 0.1% with hepatic enzyme alterations.

Dosage & Administration
Hypertension
Initial Therapy: In patients with uncomplicated initial dose is 10 mg once a day. Dosage should be adjusted according to blood pressure response. The usual dosage range is 20 to 40 mg per day administered in a single daily dose.
The antihypertensive effect may diminish toward the end of the dosage 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. Doses up to 80 mg have been used but do not appear to give greater effect. If blood pressure is not controlled with GAPRIL alone, a low dose or a diuretic may be added. Hydrochlorothiazide, 12.5 mg has been shown to provide an additive effect. After the addition or a diuretic, it may be possible to reduce the dose of GAPRIL.

Diuretic Treated Patients: In hypertensive patients who are currently being treated with a diuretic, symptomatic hypotension may occur occasionally following the initial dose of GAPRIL. The diuretic should be discontinued, if possible, for two to three days before beginning therapy with GAPRIL to reduce the likelihood of hypotension.
The dosage of GAPRIL should be adjusted according to blood pressure response. If the patient's blood pressure is not controlled with GAPRIL alone, diuretic therapy may be resumed as described above.
If the diuretic cannot be discontinued, an initial dose of 5 mg should be used under medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour.
Concomitant administration of GAPRIL with potassium supplements, potassium salt substitutes, or potassium-sparing diuretics may lead to increases of serum potassium.

Dosage Adjustment in Renal Impairment: The usual dose or GAPRIL (10 mg) is recommended for patients with creatinine clearance > 30 mL/min (serum creatinine of up to approximately 3 mg/dL). For patients with creatinine clearance ε10 mL/min δ30 mL/min (serum creatinine ε3 mg/dL). The first dose is 15 mg once daily. For patients with creatinine clearance

Heart Failure
GAPRIL is indicated as adjunctive therapy with diuretics with diuretics and (usually) digitalis. The recommended starting dose is 5 mg once e day. When initiating treatment with lisinopril in patients with heart failure, the initial dose should be administered under medical observation, especially in those patients with low blood pressure (systolic blood pressure below 100 mmHg). The mean peak blood pressure lowering occurs six to eight hours after dosing. Observation should continue until blood pressure is stable. The concomitant diuretic dose should be reduced, if possible, to help minimize hypovolemia which may contribute to hypotension.
The appearance of hypotension after the initial dose of GAPRIL does not preclude subsequent careful dose titration with the drug, following effective management of the hypotension. The usual effective dosage range is 5 to 40 mg per day administered as a single daily dose. The dose of GAPRIL can be increased by increments of no greater than 10 mg, at intervals of no less than 2 weeks to the highest tolerated dose, up to a maximum of 40 mg daily. Dose adjustment should be based on the clinical response of individual patients.

Dossage Adjustment in Patients with Heart Failure and Renal Impairment or Hyponatremia: In patients with heart failure who have hyponatremia (serum sodium 3 mg/dL), therapy with GAPRIL should be initiated at a dose of 2.5 mg once a day under close medical supervision.

Acute Myocardial Infarction
In hemodynamically stable patients within 24 hours of the onset of symptoms of acute myocardial infarction, the first dose of GAPRIL is 4 mg given orally, followed by 5 mg after 48 hours and then 10 mg of GAPRIL once daily. Dosing should continue for six weeks. Patients should receive, as appropriate, the standard recommended treatments such as thrombolytic, aspirin, and beta-blockers.
Patients with a low systolic blood pressure (δ120 mmHg) when treatment is started or during the first 3 days after the infarct should be given a lower 2.5 mg oral dose of GAPRIL. If hypotension occurs (systolic blood pressure δ100 mmHg) a daily maintenance dose of 5 mg may be given with temporary reductions to 2.5 mg if needed. If prolonged hypotension occurs (systolic blood pressure
For patients who develop symptoms of heart failure, see DOSAGE AND ADMINISTRATION, Heart Failure.

Dosage Adjustment in Patients with Myocardial Infarction with Renal Impairment: In acute myocardial infarction, treatment with Lisinopril should be initiated with caution in evidence of renal dysfunction, defined as serum creatinine concentration exceeding 2 mg/dL. No evaluation of dosing adjustments in myocardial infarction patients with severe renal impairment has been performed.

Use in Elderly
In general, the clinical response with similar in younger and older patients given similar doses of GAPRIL. 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.

Pediatric Hypertensive Patients above 6 Years of age
The usual recommended starting dose is 0.07 mg/kg once daily (up to 5 mg total). Dosage should be adjusted according to blood pressure response. Doses above 0.61 mg/kg (or in excess of 40 mg) have not been studied in pediatric patients.
GAPRIL is not recommend in pediatric patients< 6 years or in patients with glomerular filtration rate <30 ml/min/1.73 min.

Storage
Store in a cool dry place below 30°C
and protect from light.

Presentation
A blister of 14 tablets in box of 28 tablets.

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