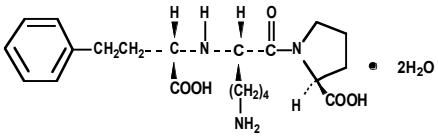
# TRUPRIL™

[LISINOPRIL TABLETS USP]

**Tablets 5mg, 10mg**

**DESCRIPTION**

TRUPRIL (Lisinopril) belongs to a class of medicines called angiotensin converting enzyme (ACE) inhibitors. Chemically it is described as (S)-1-[*N*2-(1-carboxy-3-phenylpropyl)-L-lysyl]-L-proline dihydrate. Its molecular formula is $C_{21}H_{31}N_3O_5.2H_2O$ and its structural formula is:




**Lisinopril dihydrate**

**QUALITATIVE AND QUANTITATIVE COMPOSITION**

TRUPRIL (Lisinopril) is available for oral administration as:

TRUPRIL (Lisinopril) Tablets 5mg
Each tablet contains:
Lisinopril USP…5mg
(as dihydrate)

TRUPRIL (Lisinopril) Tablets 10mg
Each tablet contains:
Lisinopril USP…10mg
(as dihydrate)

**CLINICAL PHARMACOLOGY**

**Mechanism of Action**

Lisinopril is a peptidyl dipeptidase inhibitor. It inhibits the angiotensin converting enzyme (ACE) that catalyses the conversion of angiotensin I to the vasoconstrictor peptide, angiotensin II. Whilst mechanism through which lisinopril lowers blood pressure is believed to be primarily suppression of the renin-angiotensin-aldosterone system. Lisinopril is antihypertensive even in patients with low-renin hypertension.

**Pharmacokinetics**

Lisinopril is slowly and incompletely absorbed following oral administration. About 25% of a given dose is absorbed on average, but the absorption varies considerably between individuals, ranging from about 6 – 60%. Peak concentrations in plasma are reported to occur after about 7 hours. Lisinopril is reported not to be significantly bound to plasma proteins. It is excreted unchanged in the urine. The effective half-life for accumulation following multiple doses is 12 hours. Lisinopril is removed by hemodialysis.

**Special Populations:**

*Hepatic Impairment*

Impairment of hepatic function in cirrhotic patients resulted in a decrease in lisinopril absorption (about 30% as determined by urinary recovery) but an increase in exposure (approximately 50%) compared to healthy subjects due to decreased clearance.

*Renal Impairment*

In mild to moderate renal impairment (creatinine clearance 30-80mL/min) mean AUC was increased by 13% only, while a 4.5-fold increase in mean AUC was observed in severe renal impairment (creatinine clearance 5-30mL/min). During 4 hours of haemodialysis, plasma lisinopril concentrations decreased on average by 60%.

*Heart Failure*

Patients with heart failure have a greater exposure of lisinopril when compared to healthy subjects (an increase in AUC on average of 125%), but based on the urinary recovery of lisinopril, there is reduced absorption of approximately 16% compared to healthy subjects.

*Elderly*

Older patients have higher blood levels and higher values for the area under the plasma concentration time curve (increased approximately 60%) compared with younger subjects

**THERAPEUTIC INDICATIONS**

TRUPRIL (Lisinopril) is indicated for:

- **Hypertension**
  The treatment of hypertension.
- **Heart failure**
  The treatment of symptomatic heart failure.
- **Acute myocardial infarction**
  Short-term (6 weeks) treatment of haemodynamically stable patients within 24 hours of an acute myocardial infarction.
- **Renal complications of diabetes mellitus**
  Treatment of renal disease in hypertensive patients with type 2 diabetes mellitus and incipient nephropathy.

**DOSAGE & ADMINISTRATION**

TRUPRIL (Lisinopril) should be administered in a single daily dose approximately the same time each day. The absorption of TRUPRIL (Lisinopril) is not affected by food. The dose should be individualised according to patient profile and blood pressure response.

**Hypertension**

TRUPRIL (Lisinopril) may be used as monotherapy or in combination with other classes of antihypertensive therapy.

*Starting dose*

In patients with hypertension the usual recommended starting dose of TRUPRIL (Lisinopril) is 10mg.
Patients with a strongly activated renin-angiotensin-aldosterone system (in particular, renovascular hypertension, salt and/or volume depletion, cardiac decompensation, or severe hypertension) may experience an excessive blood pressure fall following the initial dose. A starting dose of 2.5-5mg is recommended in such patients and the initiation of treatment should take place under medical supervision.

*Maintenance dose*

The usual effective maintenance dosage is 20mg administered in a single daily dose. In general if the desired therapeutic effect cannot be achieved in a period of 2 to 4 weeks on a certain dose level, the dose can be further increased up to 80mg daily, if necessary.

*Diuretic-treated patients*

Patient taking diuretics should have the diuretic withdrawn 2 to 3 days before lisinopril is started and resumed if required; if this is not possible, an initial dose of 5mg once daily should be given.

*Dosage adjustment in renal impairment*

In patients with renal impairment, the initial dose of lisinopril should be reduced depending on the creatinine clearance (CC) as follows:

- CC 31 to 80mL/minute: 5 to 10mg once daily
- CC 10 to 30mL/minute: 2.5 to 5mg once daily
- CC less than 10mL/minute or on dialysis: 2.5mg once daily

The dose should be adjusted according to the response, to a maximum of 40mg once daily.

**Heart failure**

In patients with symptomatic heart failure, TRUPRIL (Lisinopril) should be used as adjunctive therapy to diuretics and, where appropriate, digitalis or beta-blockers. TRUPRIL (Lisinopril) may be initiated at a starting dose of 2.5mg once a day, which should be administered under medical supervision to determine the initial effect on the blood pressure. The dose of TRUPRIL (Lisinopril) should be increased:

- By increments of no greater than 10mg
- At intervals of no less than 2 weeks
- To the highest dose tolerated by the patient up to a maximum of 35mg once daily.

Dose adjustment should be based on the clinical response of individual patients.

**Acute myocardial infarction**

*Starting dose*

Treatment with lisinopril may be started within 24 hours of the onset of symptoms in an initial dose of 5mg once daily for two days, and then increased to 10mg once daily. An initial dose of 2.5mg once daily is recommended for patients with a low systolic blood pressure.

*Maintenance dose*

The maintenance dose is 10mg once daily. If hypotension occurs (systolic blood pressure less than or equal to 100mmHg) a daily maintenance dose of 5mg may be given with temporary reductions to 2.5mg if needed. If prolonged hypotension occurs (systolic blood pressure less than 90mmHg for more than 1 hour) TRUPRIL (Lisinopril) should be withdrawn.
Treatment should continue for 6 weeks and then the patient should be re-evaluated. Patients who develop symptoms of heart failure should continue with TRUPRIL (Lisinopril).
Patients should receive, as appropriate, the standard recommended treatments such as thrombolytics, aspirin and beta-blockers

**Renal complications of diabetes mellitus**

The initial dose is 2.5mg once daily. In normotensive type 1 diabetics the maintenance dose is 10mg daily, increased to 20mg daily, if necessary to achieve a sitting diastolic blood pressure below 75mmHg. In hypertensive type 2 diabetics, the dose should be adjusted to achieve a sitting diastolic pressure below 90mmHg

**Pediatric hypertensive patients ≥ 3 to 6 years of age**

The usual recommended starting dose is 0.07mg/kg once daily (up to 5mg total). Dosage should be adjusted according to blood pressure response. Doses above 0.61mg/kg (or in excess of 40mg) have not been studied in pediatric patients.

**CONTRAINDICATIONS**

Lisinopril is contraindicated in patients:

- With hypersensitivity to lisinopril, to any of the excipients or any other angiotensin converting enzyme (ACE) inhibitor.
- With a history of angioedema associated with previous ACE inhibitor therapy.
- With hereditary or idiopathic angioedema.
- Who are pregnant.

**ADVERSE REACTIONS**

Lisinopril is generally well tolerated however following undesirable effects have been observed and reported during treatment with lisinopril and other ACE inhibitors.
**Common:** Dizziness, headache, orthostatic effects (including hypotension), cough, diarrhea, nausea, vomiting.
**Uncommon:** Mood alterations, paraesthesia, vertigo, taste disturbance, sleep

disturbances, myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients, palpitations, tachycardia. Raynaud's phenomenon, rhinitis, abdominal pain and indigestion, rash, pruritus, impotence, fatigue, asthenia, increase in blood urea, increase in serum creatinine, increase in liver enzymes, hyperkalaemia.
**Rare:** Decrease in hemoglobin, decrease in hematocrit, mental confusion, dry mouth, hypersensitivity/angioneurotic edema: angioneurotic edema of the face, extremities, lips, tongue, glottis, and/or larynx, urticaria, alopecia, psoriasis, uraemia, acute renal failure.
**Very rare:** Bone marrow depression, anaemia, thrombocytopenia, leucopenia, neutropenia, agranulocytosis, haemolytic anaemia, lymphadenopathy, autoimmune disease, hypoglycemia, bronchospasm, sinusitis, allergic alveolitis/eosinophilic pneumonia, pancreatitis, intestinal angioedema, hepatitis - either hepatocellular or cholestatic, jaundice and hepatic failure, diaphoresis, pemphigus, toxic epidermal necrolysis, Stevens-Johnson Syndrome, erythema multiforme, oliguria/anuria, gynaecomastia, increase in serum bilirubin, hyponatremia.

**PRECAUTIONS**
**Angioedema**
Lisinopril therapy should be immediately discontinued in patients presenting with angioedema; appropriate anti-histamine/corticosteroid therapy and monitoring should be provided until complete and sustained resolution of all signs and symptoms has occurred.
People who have had angioedema caused by other substances may be at increased risk of angioedema while receiving an ACE inhibitor such as lisinopril.

**Low blood pressure**
Occasionally, blood pressure drops too low after taking lisinopril. This usually happens after the first or second dose or when the dose is increased. It is more likely to occur in those who take diuretics, have a salt-restricted diet, are on dialysis, or are suffering from diarrhoea or vomiting. In patients at increased risk of symptomatic hypotension, initiation of therapy and dose adjustment should be closely monitored.
If hypotension occurs during treatment following acute myocardial infarction, consideration should be given to lisinopril discontinuation.
In some patients with congestive heart failure who have normal or low blood pressure, additional lowering of systemic blood pressure may occur with lisinopril. If hypotension occurs, a reduction of dose or discontinuation of therapy should be considered.

**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.

**Surgery or 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.

**Anaphylactoid reactions in hemodialysis patients**
Anaphylactoid reactions have been reported in patients dialysed with high flux membranes and treated concomitantly with an ACE inhibitor. In these patients consideration should be given to using a different type of dialysis membrane or different class of antihypertensive agent.

**Desensitisation**
Patients receiving ACE inhibitors during desensitisation treatment (e.g. hymenoptera venom) have sustained anaphylactoid reactions. These reactions have been avoided when ACE inhibitors were temporarily withheld prior to each desensitisation.

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

**Neutropenia/agranulocytosis**
Lisinopril should be used with caution in patients with collagen vascular disease, especially if there is pre-existing impaired renal function. If lisinopril is used in such patients, periodic monitoring of white blood cell counts is advised and patients should be instructed to report any sign of infection.

**Renal function impairment.**
- In some patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney, who have been treated with ACE inhibitors, increases of blood urea and serum creatinine, usually reversible upon discontinuation of therapy, have been seen. This is especially likely in patients with renal insufficiency.
- Dosage reduction and/or discontinuation of the diuretic and/or lisinopril may be required if there is increase in blood urea and serum creatinine.
- In acute myocardial infarction, treatment with lisinopril should not be initiated in patients with evidence of renal dysfunction, defined as serum creatinine concentration exceeding 177micromol/L and/or proteinuria exceeding 500mg/24h. If renal dysfunction develops during treatment with lisinopril (serum creatinine concentration exceeding 265micromol/L or a doubling from the pre treatment value) the withdrawal of lisinopril should then be considered.

**Nursing mothers**
It is not known whether lisinopril is excreted into human breast milk. Because many drugs are excreted in human milk and because of the potential for adverse reactions in nursing infants from ACE inhibitors, 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**
There are no data on the effect of lisinopril on blood pressure in pediatric patients under the age 6 or in pediatric patients.

**DRUG INTERACTIONS**
*Diuretics*
Antihypertensive effect of lisinopril is potentiated with the addition of diuretics.

*Potassium supplements, potassium-sparing diuretics or potassium-containing salt substitutes*
The use of potassium supplements, potassium-sparing diuretics (e.g. spironolactone, triamterene or amiloride) or potassium-containing salt substitutes, particularly in patients with impaired renal function, may lead to a significant increase in serum potassium. If lisinopril is given with a potassium-losing diuretic, diuretic-induced hypokalemia may be ameliorated.

*Lithium*
Use of lisinopril with lithium is not recommended, but if the combination proves necessary, careful monitoring of serum lithium levels should be performed.

*Non steroidal anti-inflammatory drugs (NSAIDs) including acetylsalicylic acid ≥ 3g/day.*
Chronic administration of NSAIDs may reduce the antihypertensive effect of an ACE inhibitor. NSAIDs and ACE inhibitors exert an additive effect on the increase in serum potassium and may result in a deterioration of renal function. These effects are usually reversible.

*Other antihypertensive agents*
Concomitant use of lisinopril with glyceryl trinitrate and other nitrates, or other vasodilators, may further reduce blood pressure.

*Tricyclic antidepressants/antipsychotics/anesthetics*
Concomitant use of certain anaesthetic medicinal products, tricyclic antidepressants and antipsychotics with ACE inhibitors may result in further reduction of blood pressure.
*Sympathomimetics*
Sympathomimetics may reduce the antihypertensive effects of ACE inhibitors.

*Antidiabetics*
Concomitant administration of ACE inhibitors and antidiabetic medicines (insulins, oral hypoglycemic agents) may cause an increased blood glucose lowering effect with risk of hypoglycemia. This phenomenon appeared to be more likely to occur during the first weeks of combined treatment and in patients with renal impairment.

**STORAGE**
Store below 30°C.
Protect from sunlight and moisture.
The expiration date refers to the product correctly stored at the required conditions.

**HOW SUPPLIED**
1. TRUPRIL (Lisinopril) 5mg tablets are available in blister packs of 14's.
2. TRUPRIL (Lisinopril) 10mg tablets are available in blister packs of 14's.

***Keep out of reach of children.***

***To be sold on prescription of a registered medical practitioner only.***

**Please read the contents carefully before use.**
**This package insert is continually updated from time to time.**

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