Drugfield Pharmaceuticals Limited

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

Kuinopril® (Lisinopril 10mg) Tablets

1. NAME OF THE MEDICINAL PRODUCT

Kuinopril® (Lisinopril 10mg) Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablets contains Lisinopril 10mg

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solid-Tablets

4. Clinical particulars

4.1 Therapeutic indications

HYPERTENSION
Kuinopril® is indicated in the treatment of all grades of essential hypertension and renovascular hypertension. Kuinopril® is used alone or in combination with other antihypertensive agents.

CONGESTIVE HEART FAILURE
Kuinopril® is indicated in the treatment of congestive heart failure as adjunctive therapy (after load reduction).

ACUTE MYOCARDIAL INFARCTION
Kuinopril® is indicated for the treatment of thermodynamically stable patients, defined as patients who are not in cardiogenic shock and who have a systolic blood pressure greater than 100mmHg.

Kuinopril® may be initiated within 24 hours of the acute myocardial infarction to prevent the subsequent development of left ventricular dysfunction or heart failure and to improve survival. Patients should receive as appropriate, the standard failure and improve survival. Patients should receive, as appropriate, the standard recommended treatments such as thrombolytics, aspirin and beta-blockers.

4.2 Posology and method of administration

Posology

Important Dosage and Administration Instructions

Use in Hypertensive Paediatric Patients aged 6-16 years

The recommended initial dose is 2.5 mg once daily in patients 20 to <50 kg, and 5 mg once daily in patients ≥50 kg. The dosage should be individually adjusted to a maximum of 20 mg daily in patients weighing 20 to <50 kg, and 40 mg in patients ≥50 kg. Doses above 0.61 mg/kg (or in excess of 40 mg) have not been studied in paediatric patients.

In children with decreased renal function, a lower starting dose or increased dosing interval should be considered.

Renal Complication of Diabetes mellitus

Treatment should be started with 2.5mg once daily and titrated to achieve the target dose. In normotensive insulin dependent diabetes mellitus patients, the dose is 10mg Lisinopril once daily which can be increased to 20mg once daily if necessary to achieve a stable diastolic blood pressure below 75mmHg.

Dosing adjustment in Renal Impairement:

Creatinine clearance (Clcr) 10-soml/minute: Administer 50% to 75% of normal dose.
Creatinine clearance (Clcr) <10ml/minute: Administer 25% to 50% of normal dose.
Hemodialysis: Dialyzable (50%).

Elderly

The initial dose is 2.5-5mg/day: increase doses 2.5-5mg/day at 1 to 2 weeks interval. Maximum daily dose is 40mg.
Patients taking diuretics should have them discontinued 2-3days prior to initiating Kuinopril if possible.

Restart diuretic after blood pressure is stable if needed. If diuretics cannot be discontinued prior to therapy, begin with 5mg with close supervision until stable blood pressure.
In patients with hyponatremia (<130Eq/L).start dose at 2.5mg/day.

Method of administration

Lisinopril tablets should be administered orally in a single daily dose. As with all other medication taken once daily, Lisinopril tablets should be taken at approximately the same time each day. The absorption of Lisinopril tablets is not affected by food.

The dose should be individualised according to patient profile and blood pressure response.

Hypertension

Lisinopril tablets 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 is 10 mg. 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 2.5-5 mg is recommended in such patients and the initiation of treatment should take place under medical supervision. A lower starting dose is required in the presence of renal impairment.

Maintenance dose

The usual effective maintenance dosage is 20 mg 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. The maximum dose used in long-term, controlled clinical trials was 80 mg/day.

Diuretic-Treated Patients

Symptomatic hypotension may occur following initiation of therapy with Lisinopril tablets. This is more likely in patients who are being treated currently with diuretics. Caution is recommended

therefore, since these patients may be volume and/or salt depleted. If possible, the diuretic should be discontinued 2 to 3 days before beginning therapy with Lisinopril tablets. In hypertensive patients in whom the diuretic cannot be discontinued, therapy with Lisinopril tablets should be initiated with a 5 mg dose. Renal function and serum potassium should be monitored. The subsequent dosage of Lisinopril tablets should be adjusted according to blood pressure response. If required, diuretic therapy may be resumed.

Dosage Adjustment In Renal Impairment

Dosage in patients with renal impairment should be based on creatinine clearance as outlined in Table 1 below.

Table 1 Dosage adjustment in renal impairment.

Creatinine Clearance (ml/min)	Starting Dose (mg/day)
Less than 10 ml/min (including patients on dialysis	2.5 mg*
10-30 ml/min	2.5-5 mg
31-80 ml/min	5-10 mg

* Dosage and/or frequency of administration should be adjusted depending on the blood pressure response.
The dosage may be titrated upward until blood pressure is controlled or to a maximum of 40 mg daily.

Use in Hypertensive Paediatric Patients aged 6-16 years

The recommended initial dose is 2.5 mg once daily in patients 20 to <50 kg, and 5 mg once daily in patients ≥50 kg. The dosage should be individually adjusted to a maximum of 20 mg daily in patients weighing 20 to <50 kg, and 40 mg in patients ≥50 kg. Doses above 0.61 mg/kg (or in excess of 40 mg) have not been studied in paediatric patients.
In children with decreased renal function, a lower starting dose or increased dosing interval should be considered.

Heart Failure

In patients with symptomatic heart failure, Lisinopril tablets should be used as adjunctive therapy to diuretics and, where appropriate, digitalis or beta-blockers. Lisinopril tablets may be initiated at a starting dose of 2.5 mg once a day, which should be administered under medical supervision to determine the initial effect on the blood pressure. The dose of Lisinopril tablets should be increased:
- By increments of no greater than 10 mg
- At intervals of no less than 2 weeks
- To the highest dose tolerated by the patient up to a maximum of 35 mg once daily.

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

Patients at high risk of symptomatic hypotension e.g. patients with salt depletion with or without hyponatraemia, patients with hypovolaemia or patients who have been receiving vigorous diuretic therapy should have these conditions corrected, if possible, prior to therapy with Lisinopril tablets. Renal function and serum potassium should be monitored.
Posology in Acute Myocardial Infarction
Patients should receive, as appropriate, the standard recommended treatments such as thrombolytics, aspirin, and beta-blockers. Intravenous or transdermal glyceryl trinitrate may be used together with Lisinopril tablets.

Starting dose (first 3 days after infarction)

Treatment with Lisinopril tablets may be started within 24 hours of the onset of symptoms. Treatment should not be started if systolic blood pressure is lower than 100 mm Hg. The first dose of Lisinopril tablets is 5 mg given orally, followed by 5 mg after 24 hours, 10 mg after 48 hours and then 10 mg once daily. Patients with a low systolic blood pressure (120 mm Hg or less) when treatment is started or during the first 3 days after the infarction should be given a lower dose - 2.5 mg orally.

In cases of renal impairment (creatinine clearance <80 ml/min), the initial Lisinopril tablets dosage should be adjusted according to the patient's creatinine clearance.

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
- Hypersensitivity to any other angiotensin converting enzyme (ACE) inhibitor.
- Hypersensitivity to any sulphonamide-derived drugs.
- History of angioedema associated with previous ACE inhibitor therapy.
- Concomitant use of Kunopril® with sacubitril/valsartan therapy. Kunopril® must not be initiated earlier than 36 hours after the last dose of sacubitril/valsartan.
- Hereditary or idiopathic angioedema.
- Second and third trimesters of pregnancy.
- Severe renal impairment (creatinine clearance < 30 ml/min).
- Anuria.
- Severe hepatic impairment.

4.4 Special warnings and precautions for use

Cough

Cough has been reported with the use of ACE inhibitors. Characteristically, the cough is non-productive, persistent and resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough.

Surgery/Anaesthesia

In patients undergoing major surgery or during anaesthesia with agents that produce hypotension, Lisinopril tablets 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.

Hyperkalaemia

Elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including Lisinopril tablets. Patients at risk for the development of hyperkalaemia include those with renal insufficiency, diabetes mellitus, or those using concomitant potassium-sparing diuretics (e.g. spironolactone, triamterene or amiloride), potassium supplements or potassium-containing salt substitutes, or those patients taking other drugs associated with increases in serum potassium (e.g. heparin, the combination trimethoprim/sulfamethoxazole also known as cotrimoxazole). If concomitant use of the above-mentioned agents is deemed appropriate, regular monitoring of serum potassium is recommended.

Diabetic patients

In diabetic patients treated with oral antidiabetic agents or insulin, glycaemic control should be closely monitored during the first month of treatment with an ACE inhibitor

Renal Function Impairment

In cases of renal impairment (creatinine clearance <80 ml/min), the initial Lisinopril tablets dosage should be adjusted according to the patient's creatinine clearance and then as a function of the patient's response to treatment. Routine monitoring of potassium and creatinine is part of normal medical practice for these patients.

In patients with heart failure, hypotension following the initiation of therapy with ACE inhibitors may lead to some further impairment in renal function. Acute renal failure, usually reversible, has been reported in this situation.

In some patients with bilateral renal artery stenosis or with a stenosis of the artery to a solitary kidney, who have been treated with angiotensin converting enzyme inhibitors, increases in blood urea and serum creatinine, usually reversible upon discontinuation of therapy, have been seen. This is especially likely in patients with renal insufficiency. If renovascular hypertension is also present there is an increased risk of severe hypotension and renal insufficiency. In these patients, treatment should be started under close medical supervision with low doses and careful dose titration. Since treatment with diuretics may be a contributory factor to the above, they should be discontinued and renal function should be monitored during the first weeks of Lisinopril tablets therapy.

Some hypertensive patients with no apparent pre-existing renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when Lisinopril tablets 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 tablets may be required.

In acute myocardial infarction, treatment with Lisinopril tablets should not be initiated in patients with evidence of renal dysfunction, defined as serum creatinine concentration exceeding 177 micromol/l and/or proteinuria exceeding 500 mg/24 h. If renal dysfunction develops during treatment with Lisinopril tablets (serum creatinine concentration exceeding 265 micromol/l or a doubling from the pre-treatment value) then the physician should consider withdrawal of Lisinopril tablets.

Hypotension In Acute Myocardial Infarction
Treatment with Lisinopril tablets must not be initiated in acute myocardial infarction patients who are at risk of further serious haemodynamic deterioration after treatment with a vasodilator. These are patients with systolic blood pressure of 100 mm Hg or lower or those in cardiogenic shock. During the first 3 days following the infarction, the dose should be reduced if the systolic blood pressure is 120 mm Hg or lower. Maintenance doses should be reduced to 5 mg or temporarily to 2.5 mg if systolic blood pressure is 100 mm Hg or lower. If hypotension persists (systolic blood pressure less than 90 mm Hg for more than 1 hour) then Lisinopril tablets should be withdrawn.

4.5 Interaction with other medicinal products and other forms of interaction

Clinically Significant Drug Interactions with Lisinopril

Antihypertensive agents

When Lisinopril tablets is combined with other antihypertensive agents (e.g. glyceryl trinitrate and other nitrates, or other vasodilators), additive falls in blood pressure may occur.

Clinical trial data has shown that dual blockade of the renin-angiotensin-aldosterone system (RAAS) through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting agent

Drugs that may increase the risk of angioedema

Concomitant treatment of ACE inhibitors with mammalian target of rapamycin (mTOR) inhibitors (e.g. temsirolimus, sirolimus, everolimus) or neutral endopeptidase (NEP) inhibitors (e.g. racecadotril) or tissue plasminogen activator may increase the risk of angioedema.

Diuretics

When a diuretic is added to the therapy of a patient receiving Lisinopril tablets the antihypertensive effect is usually additive. Patients already on diuretics and especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure when Lisinopril tablets is added. The possibility of symptomatic hypotension with Lisinopril tablets can be minimised by discontinuing the diuretic prior to initiation of treatment with Lisinopril tablets.

Potassium supplements, potassium-sparing diuretics or potassium-containing salt substitutes and other drugs that may increase serum potassium levels

Although in clinical trials, serum potassium usually remained within normal limits, hyperkalaemia did occur in some patients. The use of potassium supplements, potassium-sparing diuretics or potassium-containing salt substitutes and other drugs that may increase serum potassium levels, particularly in patients with impaired renal function, may lead to a significant increase in serum potassium.

Monitoring of potassium should be undertaken as appropriate. If Lisinopril is given with a potassium losing diuretic, diuretic induced hypokalaemia may be ameliorated.

Ciclosporin

Hyperkalaemia may occur during concomitant use of ACE inhibitors with ciclosporin. Monitoring of serum potassium is recommended.

Heparin

Hyperkalaemia may occur during concomitant use of ACE inhibitors with heparin. Monitoring of serum potassium is recommended.

Lithium

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors. Concomitant use of thiazide diuretics may increase the risk of lithium toxicity and enhance the already increased lithium toxicity with ACE inhibitors. Use of Lisinopril tablets 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

When ACE-inhibitors are administered simultaneously with non-steroidal anti-inflammatory drugs (i.e. acetylsalicylic acid at anti-inflammatory dosage regimens, COX-2 inhibitors and non-selective NSAIDs), attenuation of the antihypertensive effect may occur. Concomitant use of ACE-inhibitors and NSAIDs may lead to an increased risk of worsening of renal function, including possible acute renal failure, and an increase in serum potassium, especially in patients with poor pre-existing renal function. These effects are usually reversible. The combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring renal function after initiation of concomitant therapy, and periodically thereafter.

Tricyclic antidepressants / Antipsychotics / Anaesthetics

Concomitant use of certain anaesthetic medicinal products, tricyclic antidepressants and antipsychotics with ACE inhibitors may result in further reduction of blood pressure.

Antidiabetics

Epidemiological studies have suggested that concomitant administration of ACE inhibitors and antidiabetic medicinal products (insulins, oral hypoglycaemic agents) may cause an increased blood glucose lowering effect with risk of hypoglycaemia. This phenomenon appeared to be more likely to occur during the first weeks of combined treatment and in patients with renal impairment.

Co-trimoxazole (trimethoprim/sulfamethoxazole)

Patients taking concomitant co-trimoxazole (trimethoprim/sulfamethoxazole) may be at increased risk of hyperkalaemia.

Acetylsalicylic acid, thrombolytics, beta-blockers, nitrates

Lisinopril tablets may be used concomitantly with acetylsalicylic acid (at cardiologic doses), thrombolytics, beta-blockers and/or nitrates.

4.6 Fertility, Pregnancy and Lactation

Pregnancy

Risk Summary

Kuinopril®- is contraindicated in pregnancy and treatment should be stopped if pregnancy is suspected. Angiotensin Converting Enzyme inhibitors (ACE) can cause foetal and neonatal morbidity and mortality when administered to pregnant women during the second and third trimesters.

Lactation

Risk Summary

There is no information available regarding the use of Lisinopril tablet during breastfeeding. Therefore, Lisinopril tablet is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.

Females and Males of Reproductive Potential

Infertility

There are no data available on male and female fertility.

4.7 Effects on ability to drive and use machines

No impairment occurred in patients receiving lisinopril. Lisinopril has no influence on the ability to drive and use machines.

4.8 Undesirable effects

The following undesirable effects have been observed and reported during treatment with lisinopril and/or hydrochlorothiazide with the following frequencies: Very common (≥1/10), Common (≥1/100 to <1/10), Uncommon (≥1/1,000 to <1/100), Rare (≥1/10,000 to <1/1,000), Very rare (<1/10,000), not known (cannot be estimated from the available data).

The most commonly reported ADRs are cough, dizziness, hypotension, and headache which may occur in 1 to 10% of treated patients. In clinical studies, side effects have usually been mild and transient, and in most instances have not required interruption of therapy.

Lisinopril:

Blood and lymphatic system disorders:	
Rare	Decreases in haemoglobin, decreases in haematocrit.
Very rare	Bone marrow depression, anaemia, thrombocytopenia, leucopenia, neutropenia, agranulocytosis (see section 4.4), haemolytic anaemia, lymphadenopathy, autoimmune disease.
Immune system disorders	
Not known	Anaphylactic/anaphylactoid reaction
Endocrine disorders	
Rare	Syndrome of inappropriate antidiuretic hormone secretion (SIADH).
Metabolism and nutrition disorders:	
Very rare	Hypoglycaemia.
Psychiatric disorders and nervous system disorders	
Common	Dizziness, headache, syncope.
Uncommon	Paraesthesia, vertigo, taste disturbance, sleep disturbances, mood alterations, depressive symptoms.
Rare	Mental confusion, Olfactory disturbance.
Not known	Hallucinations.
Cardiac and vascular disorders	
Common	Orthostatic effects (including orthostatic hypotension).
Uncommon	Myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients (see section 4.4), palpitations, tachycardia, Raynaud's syndrome.
Not known	Flushing.
Respiratory, thoracic and mediastinal disorders	
Common	Cough (see section 4.4).
Uncommon	Rhinitis.
Very rare	Bronchospasm, sinusitis, allergic alveolitis/eosinophilic pneumonia.
Gastrointestinal disorders	
Common	Diarrhoea, vomiting.
Uncommon	Nausea, abdominal pain and indigestion.
Rare	Dry mouth.
Very rare	Pancreatitis, intestinal angioedema.

Hepatobiliary disorders	
Uncommon	Elevated liver enzymes and bilirubin.
Very rare	Hepatitis - either hepatocellular or cholestatic, jaundice and hepatic failure (see section 4.4).*
Skin and subcutaneous tissue disorders	
Uncommon	Rash, pruritus.
Rare	Hypersensitivity/angioneurotic oedema: angioneurotic oedema of the face, extremities, lips, tongue, glottis, and/or larynx (see section 4.4), urticaria, alopecia, psoriasis.
Very rare	Diaphoresis, pemphigus, toxic epidermal necrolysis, Stevens-Johnson Syndrome, erythema multiforme, cutaneous pseudolymphoma.**
Renal and urinary disorders	
Common	Renal dysfunction.
Rare	Uraemia, acute renal failure.
Very rare	Oliguria/anuria.
Reproductive system and breast disorders	
Uncommon	Impotence.
Rare	Gynaecomastia.
General disorders and administration site conditions	
Uncommon	Asthenia, fatigue.
Investigations	
Uncommon	Increases in blood urea, increases in serum creatinine, hyperkalaemia.
Rare	Hyponatraemia.

* Very rarely, it has been reported that in some patients the undesirable development of hepatitis has progressed to hepatic failure. Patients receiving lisinopril/hydrochlorothiazide combination who develop jaundice or marked elevations of hepatic enzymes should discontinue lisinopril/hydrochlorothiazide combination and receive appropriate medical follow up.

** 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 manifestations may occur.

4.9 Overdose

Limited data are available for overdose in humans. Symptoms associated with overdosage of ACE inhibitors may include hypotension, circulatory shock, electrolyte disturbances, renal failure, hyperventilation, tachycardia, palpitations, bradycardia, dizziness, anxiety and cough. The recommended treatment of overdose is intravenous infusion of normal saline solution. If hypotension occurs, the patient should be placed in the shock position. If available, treatment with angiotensin II infusion and/or intravenous catecholamines may also be considered. If ingestion is recent, take measures aimed at eliminating Lisinopril tablets (e.g., emesis, gastric lavage, administration of absorbents and sodium sulphate). Lisinopril tablets may be removed from the general circulation by haemodialysis. Pacemaker therapy is indicated for therapy-resistant bradycardia. Vital signs, serum electrolytes and creatinine concentrations should be monitored frequently.

5. PHARMACOLOGICAL PROPERTIES

5.1 **Pharmacological Properties**

Pharmacotherapeutic group: ACE-inhibitor

Lisinopril

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. Angiotensin II also stimulates aldosterone secretion by the adrenal cortex. Inhibition of ACE results in decreased concentrations of angiotensin II which results in decreased vasopressor activity and reduced aldosterone secretion. The latter decrease may result in an increase in serum potassium concentration.

Pharmacodynamic effects

While the 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. ACE is identical to kininase II, an enzyme that degrades bradykinin. Whether increased levels of bradykinin, a potent vasodilatory peptide, play a role in the therapeutic effects of lisinopril remains to be elucidated.

Clinical efficacy and safety

Renin-angiotensin system (RAS)-acting agents

Two large randomised, controlled trials (ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) and VA NEPHRON-D (The Veterans Affairs Nephropathy in Diabetes)) have examined the use of the combination of an ACE-inhibitor with an angiotensin II receptor blocker.

ONTARGET was a study conducted in patients with a history of cardiovascular or cerebrovascular disease, or type 2 diabetes mellitus accompanied by evidence of end organ damage. VA NEPHRON-D was a study in patients with type 2 diabetes mellitus and diabetic nephropathy.

These studies have shown no significant beneficial effect on renal and/or cardiovascular outcomes and mortality, while an increased risk of hyperkalaemia, acute kidney injury and/or hypotension as compared to monotherapy was observed. Given their similar pharmacodynamic properties, these results are also relevant for other ACE-inhibitors and angiotensin II receptor blockers.

ACE-inhibitors and angiotensin II receptor blockers should therefore not be used concomitantly in patients with diabetic nephropathy.

ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints) was a study designed to test the benefit of adding aliskiren to a standard therapy of an ACE-inhibitor or an angiotensin II receptor blocker in patients with type 2 diabetes mellitus and chronic kidney disease, cardiovascular disease, or both. The study was terminated early because of an increased risk of adverse outcomes. Cardiovascular death and stroke were both numerically more frequent in the aliskiren group than in the placebo group and adverse events and serious adverse events of interest (hyperkalaemia, hypotension and renal dysfunction) were more frequently reported in the aliskiren group than in the placebo group.

5.2 Pharmacokinetic properties

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.

Lisinopril

Absorption

Following oral administration of lisinopril, peak serum concentrations 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. Based on urinary recovery, the mean extent of absorption of lisinopril is approximately 25%, with interpatient variability (6-60%) at all doses tested (5-80 mg). The absolute bioavailability is reduced approximately 16% in patients with heart failure.

Lisinopril absorption is not affected by the presence of food.

Distribution

Lisinopril does not appear to bind to other serum proteins other than to circulating angiotensin-converting enzyme (ACE).

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

Elimination

Lisinopril does not undergo metabolism and absorbed drug is excreted unchanged entirely in the urine.

On multiple dosing lisinopril has an effective half-life of accumulation of 12.6 hours. The clearance of lisinopril in healthy subjects is approximately 50 ml/min. 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.

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

Impaired renal function decreases elimination of lisinopril, which is excreted via the kidneys, but this decrease becomes clinically important only when the glomerular filtration rate is below 30 ml/min.

Table 1 Pharmacokinetic parameters of lisinopril to different groups of renal patients after administration of a multiple 5 mg dose

Renal Function Measured by creatinine clearance	**n**	**Cmax (ng/ml)**	**Tmax (hr)**	**AUC (0-24 hrs) (ng/hr/ml)**	**$t_{1/2}$ (hr)**
>80 ml/min	6	40.3	6	492+/-172	6.0+/-1.1
30-80 ml/min	6	36.6	8	555+/-364	11.8+/-1.9
5-30 ml/min	6	106.7	8	2228+/-938	19.5+/-5.2

With a creatinine clearance of 30-80ml/min, mean AUC was increased by 13% only, while a 4-5 fold increase in mean AUC was observed with creatinine clearance of 5-30ml/min.

Lisinopril can be removed by dialysis. During 4 hours of haemodialysis, plasma lisinopril concentrations decreased on average by 60%, with a dialysis clearance between 40 and 55 ml/min.

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

Elderly patients have higher blood levels and higher values for the area under the plasma concentration time curve (increased approximately 60%) than younger patients.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of general pharmacology, repeated dose toxicity, genotoxicity, and carcinogenic potential. Angiotensin converting enzyme inhibitors, as a class, have been shown to induce adverse effects on the late foetal development, resulting in foetal death and congenital effects, in particular affecting the skull. Foetotoxicity, intrauterine growth retardation and patent ductus arteriosus have also been reported. These developmental anomalies are thought to be partly due to a direct action of ACE inhibitors on the foetal renin-angiotensin system and partly due to ischaemia resulting from maternal hypotension and decreases in foetal-placental blood flow and oxygen/nutrients delivery to the foetus.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Micro-crystalline Cellulose
Calcium Phosphate Dibasic
Erythrocine Lake
Sodium Starch Glycolate
Polyvinyl Pyrolidone (PK-30)
Corn Starch
Magnesium Stearate

6.2 Incompatibilities

Not applicable

6.3 Shelf life

48 Months

6.4 Special precautions for storage

Store below 30°C. Protect from light and moisture. Store tablets in blisters in the provided carton.

6.5 Nature and contents of container and special equipment for use, administration or implantation

The tablets are packed in transparent PVC-PVdC/aluminium blisters in cardboard outer packaging.

Kuinopril® Tablet is available in blister of 28 packed in hardboard carbon carton with leaf enclosed

6.6 Special precautions for disposal and other handling

No special requirements.

7. APPLICANT/MANUFACTURER

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