Corace® TABLETS
(Lisinopril)

کوریس ٹیبلیٹس
(لزینوپرل)

WARNING: FETAL TOXICITY
When pregnancy is detected, discontinue as soon as possible. Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing foetus

QUALITATIVE AND QUANTITATIVE COMPOSITION
Corace 5mg Tablets
Each tablet contains:
Lisinopril USP…….5mg as Lisinopril Dihydrate
(Product specs: USP)

Corace 10mg Tablets
Each tablet contains:
Lisinopril USP…….10mg as Lisinopril Dihydrate
(Product specs: USP)

Corace 20mg Tablets
Each tablet contains:
Lisinopril USP…….20mg as Lisinopril Dihydrate
(Product specs: USP)

PHARMACEUTICAL FORM
Tablets

CLINICAL PARTICULARS
Therapeutic indications
Corace tablets are indicated for:
- Treatment of hypertension.
- Treatment of symptomatic heart failure.
- Short-term (6 weeks) treatment of haemodynamically stable patients within 24 hours of an acute myocardial infarction.
- Treatment of renal disease in hypertensive patients with Type 2 diabetes mellitus and incipient nephropathy

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

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

Hypertension
Corace 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 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 2.5mg-5mg 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 20mg administered in a single daily dose.

Diuretic-Treated Patients
Symptomatic hypotension may occur following initiation of therapy with Lisinopril. 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.
In hypertensive patients in whom the diuretic cannot be discontinued, therapy with Lisinopril should be initiated with a 5mg dose. Renal function and serum potassium should be monitored. The subsequent dosage of Lisinopril 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

Table: Dosage adjustment in renal impairment

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

* 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 40mg daily.

Use in Hypertensive Pediatric Patients aged 6-16 year
The recommended initial dose is 2.5mg once daily in patients 20 to <50 kg, and 5mg once daily in patients ≥50 kg. The dosage should be individually adjusted to a maximum of 20mg daily in patients weighing 20 to <50 kg, and 40mg in patients ≥50 kg.
Doses above 0.61mg/kg (or in excess of 40mg) have not been studied in pediatric 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 should be used as adjunctive therapy to diuretics and, where appropriate, digitalis or beta-blockers. 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 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. 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. Renal function and serum potassium should be monitored.

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. Starting dose (first 3 days after infarction), treatment with Lisinopril 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 is 5mg given orally, followed by 5mg after 24 hours, 10mg after 48 hours and then 10mg 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 - 2.5mg orally.
In cases of renal impairment (creatinine clearance <80 mL/min), the initial Lisinopril dosage should be adjusted according to the patient's creatinine clearance.

Maintenance dose
The maintenance dose is 10mg once daily. If hypotension occurs (systolic blood pressure less than or equal to 100 mm Hg) 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 90 mm Hg for more than 1 hour) 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 Lisinopril.

Renal Complications of Diabetes Mellitus
In hypertensive patients with type 2 diabetes mellitus and incipient nephropathy, the dose is 10mg Lisinopril once daily which can be increased to 20mg once daily, if necessary, to achieve a sitting diastolic blood pressure below 90 mm Hg.
In cases of renal impairment (creatinine clearance <80 mL/min), the initial Lisinopril dosage should be adjusted according to the patient's creatinine clearance.

Pediatric population
There is limited efficacy and safety experience in hypertensive children >6 years old, but no experience in other indications. Lisinopril is not recommended in children in other indications than hypertension.
Lisinopril is not recommended in children below the age of 6, or in children with severe renal impairment (GFR <30mL/min/1.73m^2).

Use in the elderly
There is no age-related change in the efficacy or safety profile of the drug.

Use in kidney transplant patients
There is no experience regarding the administration of Lisinopril in patients with recent kidney transplantation.

Contraindications
- Hypersensitivity to Lisinopril, or any other angiotensin converting enzyme (ACE) inhibitor
- History of angioedema associated with previous ACE inhibitor therapy.
- Hereditary or idiopathic angioedema.
- Second and third trimester of pregnancy.
- The concomitant use of Lisinopril with aliskiren containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 mL/min/1.73 m^2).
- Lisinopril must not be initiated earlier than 36 hours after the last dose of sacubitril/valsartan.

Special warnings and precautions for use
Symptomatic Hypotension: In some patients with heart failure who have normal or low blood pressure, additional lowering of systemic blood pressure may occur with Lisinopril. If hypotension becomes symptomatic, a reduction of dose or discontinuation of Lisinopril may be necessary.

Hypotension in Acute Myocardial Infarction: Treatment with Lisinopril must not be initiated in acute myocardial infarction patients who are at risk of further serious haemodynamic deterioration after treatment with a vasodilator.

Aortic and mitral valve stenosis / hypertrophic cardiomyopathy: As with other ACE inhibitors, Lisinopril should be given with caution to patients with mitral valve stenosis and obstruction in the outflow of the left ventricle such as aortic stenosis or hypertrophic cardiomyopathy.

Renal Function Impairment: In cases of renal impairment (creatinine clearance <80 mL/min), the initial Lisinopril dosage should be adjusted according to the patient's creatinine clearance and then as a function of the patient's response to treatment.

Hypersensitivity/Angioedema: Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported uncommonly in patients treated with angiotensin converting enzyme inhibitors, including Lisinopril. This may occur at any time during therapy. Concomitant use of ACE inhibitors with sacubitril/valsartan is contraindicated due to the increased risk of angioedema.

Anaphylactoid reactions in Haemodialysis Patients: Anaphylactic reactions have been reported. In these patients consideration should be given to using a different type of dialysis membrane or different class of antihypertensive agent.

Anaphylactoid reactions during low-density lipoproteins (LDL) apheresis: These reactions were avoided by temporarily withholding ACE inhibitor therapy prior to each apheresis.

Desensitisation: Patients receiving ACE inhibitors during desensitisation treatment (e.g. hymenoptera venom) have sustained anaphylactoid reactions.

Hepatic failure: Patients receiving Lisinopril who develop jaundice or marked elevations of hepatic enzymes should discontinue Lisinopril.

Neutropenia/Agranulocytosis: Neutropenia/agranulocytosis, thrombocytopenia and Anemia have been reported in patients receiving ACE inhibitors. In patients with normal renal function and no other complicating factors, neutropenia occurs rarely. Neutropenia and agranulocytosis are reversible after discontinuation of the ACE inhibitor.

Dual blockade of the renin angiotensin aldosterone system (RAAS): Dual blockade of RAAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is not recommended.

Cough: Cough has been reported with the use of ACE inhibitors. Characteristically, the cough is non-productive, persistent and resolves after discontinuation of therapy.

Race: Lisinopril may be less effective in lowering blood pressure in black patients than in non-blacks, possibly because of a higher prevalence of low-renin states in the black hypertensive population.

Surgery/Anaesthesia: In patients undergoing major surgery or during anaesthesia 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.

Hyperkalaemia & Diabetic patients: ACE inhibitors can cause hyperkalaemia because they inhibit the release of aldosterone. In diabetic patients it should be closely monitored during the first month of treatment with an ACE inhibitor interaction.

Lithium: The combination of lithium and Lisinopril is generally not recommended.

Pregnancy: When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately.

Interaction with other medicinal products and other forms of interaction
Antihypertensive agents: When Lisinopril is combined with other antihypertensive agents

(e.g. glyceryl trinitrate and other nitrates, or other vasodilators), additive falls in blood pressure may occur. 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.

Diuretics: When a diuretic is added to the therapy of a patient receiving Lisinopril the antihypertensive effect is usually additive.

Cyclosporine & Heparin: Hyperkalaemia may occur during concomitant use of ACE inhibitors with cyclosporine. Monitoring of serum potassium is recommended.

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 medicinal products (NSAIDs) including acetylsalicylic acid ≥ 3g/day: 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.

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.

Gold: Nitritoid reactions (symptoms of vasodilatation including flushing, nausea, dizziness and hypotension, which can be very severe) following injectable gold (for example, sodium aurothiomalate) have been reported more frequently in patients receiving ACE inhibitor therapy.

Sympathomimetic: Sympathomimetic may reduce the antihypertensive effects of ACE inhibitors.

Tissue Plasminogen Activators: Concomitant treatment with tissue plasminogen activators may increase the risk of angioedema.

Acetylsalicylic acid, thrombolytic, beta-blockers, nitrates: Lisinopril may be used concomitantly with acetylsalicylic acid, thrombolytic, beta-blockers and/or nitrates.

Medicines increasing the risk of angioedema: Concomitant use of ACE inhibitors with sacubitril/valsartan is contraindicated as this increases the risk of angioedema.
Concomitant use of ACE inhibitors with racecadotril, mTOR inhibitors may lead to an increased risk for angioedema.

Fertility, Pregnancy and lactation
Pregnancy
The use of ACE inhibitors is not recommended during the first trimester of pregnancy
The use of ACE inhibitors is contra-indicated during the second and third trimester of pregnancy. Infants whose mothers have taken ACE inhibitors should be closely observed for hypotension

Lactation
Lisinopril is not recommended and alternative treatments with better established safety profiles during breastfeeding are preferable, especially while nursing a new-born or preterm infant.

Effects on ability to drive and use machines
When driving vehicles or operating machines it should be taken into account that occasionally dizziness or tiredness may occur.

Undesirable effects
The following undesirable effects have been observed and reported during treatment with Lisinopril and other ACE inhibitors 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)

MedDRA System Organ Class	Frequency	Undesirable Effects
Blood and the lymphatic system disorders	Rare	Decreases in haemoglobin, Decreases in haematocrit.
	Very rare	Bone marrow depression, Anemia, thrombocytopenia, leukopenia, neutropenia, agranulocytosis haemolytic Anemia, lymphadenopathy, autoimmune disease.
Immune system disorders	Not known	Anaphylactic/anaphylactic reaction
Metabolism and nutrition disorders	Very rare	Hypoglycaemia
Nervous system and psychiatric disorders	Common	Dizziness, headache
	Uncommon	Mood alterations, paraesthesia, vertigo, taste disturbance, sleep disturbances, hallucinations
	Rare	Mental confusion, olfactory disturbance
	Frequency not known	Depressive symptoms, syncope
Cardiac and vascular disorders	Common	Orthostatic effects (including hypotension)
	Uncommon	Myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients palpitations, tachycardia. Raynaud's phenomenon.
Respiratory, thoracic and mediastinal disorders	Common	Cough
	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, hepatitis - either hepatocellular or cholestatic, jaundice and hepatic failure
Skin and subcutaneous tissue disorders	Uncommon	Rash, pruritus
	Rare	Urticaria,alopecia,psoriasis, hypersensitivity/angioneurotic Oedema: Angioneurotic oedema of the face, extremities, lips, tongue, glottis, and/or larynx
	Very rare	Sweating, pemphigus, toxic epidermal necrolysis, Stevens-Johnson Syndrome, erythema multiforme, cutaneous pseudolymphoma.
Renal and urinary disorders	Common	Renal dysfunction
	Rare	Uraemia, acute renalfailure
	Very rare	Oliguria/anuria
Endocrine disorders	Rare	Syndrome of inappropriate antidiuretic hormone secretion (SIADH).
Reproductive system and breast disorders	Uncommon	Impotence
	Rare	Gynaecomastia
General disorders and administration site conditions	Uncommon	Fatigue, asthenia
Investigations	Uncommon	Increases in blood urea, increases in serum creatinine, increases in liver enzymes, hyperkalaemia.
	Rare	Increases in serum bilirubin, hyponatraemia

Overdose
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 ingestion is recent, take measures aimed at eliminating Lisinopril .Vital signs, serum electrolytes and creatinine concentrations should be monitored frequently.

PHARMACOLOGICAL PROPERTIES
Pharmacodynamic properties
Pharmacotherapeutic group: Angiotensin-converting enzyme inhibitors, ATC code: C09A A03.

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 later decrease may result in an increase in serum potassium concentration.

Pharmacokinetic properties

Lisinopril is an orally active non-sulphydryl-containing ACE inhibitor.

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 of 6-60% over the specified dose range. 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 be bound to serum proteins other than to circulating angiotensin converting enzyme (ACE).

Elimination

Lisinopril does not undergo metabolism and is excreted entirely unchanged into the urine. On multiple dosing lisinopril has an effective half-life of accumulation of 12.6 hours.

Hepatic impairment

Impairment of hepatic function in cirrhotic patients resulted in a decrease in lisinopril absorption.

Renal impairment

Impaired renal function decreases elimination of lisinopril, which is excreted via the kidneys, 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, but based on the urinary recovery of lisinopril, there is reduced absorption.

PHARMACEUTICAL PROPERTIES

Incompatibilities

Not Applicable

Shelf life: 3 years

Special precautions for storage

Protect from moisture, freezing and excessive heat,
store at controlled room temperature (20°C-25°C).
The expiration date refers to the product correctly stored at the required condition.
Keep out of the reach of children.
To be sold on the prescription of a registered medical practitioner only.

Presentation

Corace 5mg Tablets: Cold Form and Cold seal (Alu Alu) blister pack of 20 Tablets
Corace 10mg Tablets: Cold Form and Cold seal (Alu Alu) blister pack of 20 Tablets
Corace 20mg Tablets: Cold Form and Cold seal (Alu Alu) blister pack of 20 Tablets

REGISTRATION HOLDER / MARKETING AUTHORIZATION HOLDER

Head Office:

Bosch Pharmaceuticals (Pvt.) Ltd.,
8, Modern Society, Tipu Sultan Road, Karachi-75350 (Pakistan)

MANUFACTURER

Bosch Pharmaceuticals (Pvt.) Ltd.,
Plot No. 221-223, Sector 23 Korangi Industrial area, Karachi, Pakistan

REGISTRATION / MARKETING AUTHORIZATION NUMBER

Corace 5mg tablets: 027175
Corace 10mg tablets: 027176
Corace 20mg tablets: 027177

DATE FROM WHICH MARKETING IS AUTHORIZED/RENEWAL OF AUTHORIZATION

24-07-2001/23-07-2021

DATE OF REVISION OF THE TEXT.

14-12-2023

ہدایات :

شدید گرمی، نمی اور جمنے سے محفوظ کمرے کے درجہ حرارت (۲۰۔۲۵ڈگری سینٹی گریڈ) پر رکھیں۔
بچوں کی پہنچ سے دُور رکھیں۔
صرف مستند ڈاکٹر کے نسخے پر فروخت کے لئے۔

Manufactured by:

Bosch Pharmaceuticals (Pvt.) Ltd.

221-223, Sector 23, Korangi Industrial Area,
Karachi - Pakistan

PNAC LAB 168 17025

Pakistan's 1st Halaal Certified