1.6.1.1 Name of the medicinal Product

Captopril Tablets 25 mg

1.6.1.1.1 strength

25 mg/tablet

1.6.1.1.2 Pharmaceutical Form

Oral tablet

1.6.1.2 Qualitative and Quantitative Composition

1.6.1.2.1 Qualitative declaration

Captopril BP

1.6.1.2.2 Quantitative declaration

Sr. No.	Ingredients Chemical Name	Specification	Standard Quantity (mg/Tablet)	Reason for Inclusion
01.	Captopril	BP	25.00	Angiotensin-Converting Enzyme Inhibitors
02.	Pregelatinized Starch (STARCH 1500)	BP	18.00	Disintegrant
03.	Lactose Monohydrate	USP/NF	60.00	Diluent
04.	Microcrystalline Cellulose (PH 102)	BP	71.00	Diluent
05.	Stearic Acid	BP	4.000	Lubricant
06.	Purified Talc	BP	2.000	Glidant

1.6.1.3 Pharmaceutical Form

Oral, Uncoated Tablet

White to off-white colored, Round Shaped, flat uncoated tablets, biscored on one side and plain on other side.

1.6.1.4 Clinical Particulars

1.6.1.4.1 Therapeutic Indications

Captopril used in the treatment of hypertension; congestive heart failure; myocardial infarction within the first 24 hours in patients with hemodynamically stable condition and post-myocardial infarction patients with left ventricular dysfunction (ejection fraction ≤ 40%). It is also used for diabetic nephropathy.

1.6.1.4.2 Posology and Method of Administration

Adults: Hypertension:

The recommended starting dose is 25-50 mg daily in two divided doses. The dose may be increased incrementally, with intervals of at least 2 weeks, to 100-150mg/day in two divided doses as needed to reach target blood pressure. Captopril may be used alone or with other antihypertensive agents, especially thiazide diuretics. A once-daily dosing regimen may be appropriate when concomitant antihypertensive medication such as thiazidediuretics is added.

In patients with a strongly active renin-angiotensin-aldosterone system (hypovolaemia, renovascular hypertension, cardiac decompensation) it is preferable to commence with a single dose of 6.25 mg or 12.5 mg. The inauguration of this treatment should preferably take place under close medical supervision. These doses will then be administered at a rate of two per day. The dosage can be gradually increased to 50mg per day in one or two doses and if necessary to 100 mg per day in one or two doses. *Heart Failure:*

The usual starting dose is 6.25mg- 12.5mg BID orTID. Titration to the maintenance dose (75 - 150mg per day) should be carried out based on patient's response, clinical status and tolerability, up to a maximum of 150mg per day in divided doses. The dose should be increased incrementally, with intervals of at least 2 weeks to evaluate patient's response.

Myocardial Infarction:

Acute phase: Treatment with captopril will be initiated in the hospital as soon as possible after the onset of signs and/or symptoms in hemodynamical\y stable patients.

A test dose of 6.25 mg is administered, then 2 hours after a dose of 12.5 mg, and 12 hours after a dose of 25 mg. The next day, captopril is administered at a dose of l00 mg per day in 2 divided doses daily for 4 weeks if the patient's hemodynamic tolerance pennits. At the end of4 weeks of treatment, the patient will be reassessed before the therapeutic decision to phase post-myocardial infarction.

Chronic treatment: If treatment with captopril did not begin in the acute phase of myocardial infarction in the first 24 hours, it is suggested to begin treatment between the 3rd and 16th day of infarction as soon as conditions initiation of treatment are met (hemodynamic stability support a possible residual ischemia). The initial dose should be low 6.25 mg followed by 12.5 mg 3 times daily for 2 days, then 25 mg 3 times daily if the patient's hemodynamic tolerance permits. The recommended dose for effective cardioprotection in the long-term treatment is 75 mg to 150 mg per day in 2 or 3 doses. If symptomatic hypotension, as in heart failure, the dose of diuretics and/or other vasodilators may be associated with reduced dose to achieve the balance of captopril. If necessary, the dose of captopril is adjusted according to the tolerance of the patient. *Diabetic nephropathy:* The recommended dose ofcaptopril for long term use to treat diabetic nephropathy is 25 mg t.i.d.

Renal Impairment: captopril is excreted primarily via the kidneys, dosage should be reduced or the dosage interval should be increased in patients with impaired renal function. When concomitant diuretic therapy is required, a loop diuretic (e.g. furosernide), rather than a thiazide diuretic, is preferred in patients with severe renal impairment. In patients with renal insufficiency, the dose of captopril is adjusted to the degree of impairment:

Creatinine clearance (ml/min/1,73 m^2)	Daily starting dose (mg)	Daily maximum dose (mg)
>40	25-50	150
21-40	25	100
10-20	12.5	75
<10	6.25	37.5

Elderly patients:

As with other antihypenensive agents, consideration should be given to initiating therapy with a lower starting dose (6.25 mg BID) in elderly patients who may have reduced renal function and other organ dysfunctions. Dosage should be titrated against the blood pressure response and kept as low as possible 10 achieve adequate control.

Children and adolescents: The efficacy and safety of captopril have not been fully established

1.6.1.4.3 Contraindications

Captopril is contraindicating in the patient with known hypersensitivity to captopril, to any of the excipients or any other ACE inhibitor. History of angioedema associated with the intake of an ACE inlubitor; hereditary/ idiopathic angioneurotic oedema; second and third trimester of pregnancy, lactation.

1.6.1.4.4 Special Warnings and Special Precautions for Use

Risk of symptomatic hypotension is more likely to occur in hypertensive patients who are volume and/or sodium depleted by vigorous diuretic therapy, dietary salt restriction, diarrhoea, vomitmg or haemodialysis. Myocardial infarction or stroke in patients with ischemic heart disease or cerebral circulatory insufficiency; angioedema of the extremities (i.e. face, lips, mucous membranes, tongue, glottis or larynx) may occur any time during treatment; elevations in serum potassium (Hyperkalaemia); neutrepenia/agranulocytosis, thrombocytopenia and anaemia; Proteinuria; non-productive cough; anaphylactoid reactions during high-flux dialysis/lipoprotein apheresis membrane exposure, sustained life-threatening anaphylactoid reactions for patients undergoing desensitising treatment with hymenoptera venom has been reported with the use of ACE inhibitor including captopril. Patients with heart failure are at higher risk of hypotension. There is an increased risk of hypotension and renal insufficiency when patients with bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney are treated with ACE inhibitors. Patients undergoing major surgery or during treatment with anesthetic agents are risk of hypotension. ACE inhibitors should be used with caution in patients with left ventricular valvular and outflow tract obstruction and avoided in cases of cardiogenic shock and haemodynamically significant obstruction.

Renal impairment: In cases of renal impairment (creatinine clearance $\leq$ 40 ml/min), the initial dosage of captopril must be adjusted according to the patient's creatinine clearance, and then as a function of the patient's response to treatment. The dose should not exceed that necessary for adequate control and should be reduced in patients with impaired renal function.

Hepatic impairment: Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and (sometimes) death.

Diabetic patients: The glycaemia levels should be closely monitored in diabetic patients previously treated with oral antidiabetic drugs or insulin, namely during the first month of treatment with an ACE inhibitor.

Pregnancy: ACE inhibitors should not be initiated during pregnancy. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started.

lactation: The use ofCaptopril in breastfeeding is not recommended for preterm infants and for the first few weeks after delivery, because of the hypothetical risk of cardiovascular and renal effects and because there is not enough clinical experience.

1.6.1.4.5 Interaction with other medicinal products and other forms of interaction

Captopril may interact with Potassium sparing diuretics (e.g. spironolactone, triamterene or amiloride), potassium supplements, or potassium• containing salt; Lithium; Estramustine; Antidiabetic agents (insulin, sulphonylureas); other anti-hypertensive agents (e.g. betablockers and long• acting calcium channel blockers); NSAIDs, salicylates in high doses (>3 g per day); Antidepressants lmipramine (tricyclics), neuroleptics; Corticosteroids, Tetracosactide (route), except hydroconisone; Allopurinol, procainamide, cytostatic or immunosuppressive agents.

1.6.1.4.6 Fertility, Pregnancy and Lactation

Pregnancy: ACE inhibitors should not be initiated during pregnancy. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started.

lactation: The use ofCaptopril in breastfeeding is not recommended for preterm infants and for the first few weeks after delivery, because of the hypothetical risk of cardiovascular and renal effects and because there is not enough clinical experience.

1.6.1.4.7 Effects on ability To Drive and use Machines

As with other antihypertensives, the ability to drive and use machines may be reduced, namely at the start of the treatment, or when posology is modified, and also when used in combination with alcohol, but these effects depend on the individual's susceptibility.

1.6.1.4.8 Undesirable Effects

The adverse effects of captopril are neutropenia/agranulocytosis, hyperkalaemia, hypoglycaemia, sleep disorders, taste impairment, dizziness, drowsiness, headache and paraesthesia, tachycardia or tachyarrhythmia, angina pectoris, palpitations, dry and irritating non-productive cough, dyspnoea, nausea, vomiting, abdominal pain, diarrhoea, constipation, dry mouth, impaired hepatic function and cholestasis (includingjaundice), pruritus with or without a rash, alopecia, angioedema, polyuria, oliguria, increased urine frequency, nephrotic syndrome, chest pain, fatigue, malaise, fever.

1.6.1.4.9 Overdose

Overdose symptoms include severe hypotension, shock, lethargy, bradycardia, electrolyte disturbance and renal failure. lfhypotension occurs, patient should be placed in supine position and sodium supplements as well as fluids should be administered immediately. Parasympathetic nervous system side effects should be treated with atropine administration. In this case cardiac pacing may be considered. Captopril may be eliminated from the circulation with haemodialysis.

1.6.1.5 Pharmacological Properties

1.6.1.5.1 Pharmacodynamics Properties

Captopril is an angiotensin converting enzyme (ACE) inhibitors of angiotensin I to angiotensin II vasoconstrictor substance. It reduced aldosterone secretion, an increase in plasma renin activity, aldosterone no longer carrying negative feedback and decrease in total peripheral

resista nce with a preferential action on muscle and renal territories, a lthough this decrease is accompanied by flu id retention or reflex tac- hycardia. The treatment o f hypertension with captopril increases arterial compliance, increased renal blood !low without significant decrease in glomerular filtration rate and a reduction in left ventricular hypertrophy. In bean fa ilure patients it reduces the workload oft he bean by venous vasodilator effect proba bly due to a change in prostaglandin metabolism decreased pre load and by decreasing total peripheral resistance decreased afterload.

1.6.1.5.2 Pharmacokinetic Properties

Oral captopril is rapidly absorbed (peak blood levels in the first hour). The amount absorbed is 75% of the administered dose is reduced by 30 to 35% by food intake, without affecting efficiency. In plasma, 30% are anached to plasma albumin. The half-life of unchanged captopril is close to 2 hours. Ca ptopril excreted in urine is approximately 95% (40 to 50% in unchanged form} of the a dministered dose of captopril. Patients with renal impairment, plasma conccntrat ionsofcaptopril were significantly higher in patients with a creatin ine clearance less than orequal to 40 mllmin. the half-life up to 30 hours. Captopril crosses the placenta. Passage into breast milk occurs in very small amounts.

1.6.1.5.3 Preclinical Safety Data

Animal studies performed during organogenesis with captopril have not shown any teratogenic effect but captopril has produced foetal toxicity in several species, including foetal mortality during late pregnancy, growth retardation and postnatal mortality in the rat. Preclinical data reveal no other specific hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicology, genotoxicity and carcinogenicity.

1.6.1.6 Pharmaceutical Particulars

1.6.1.6.1 List of Excipients

Pregelatinized Starch (STARCH 1500) BP

Lactose Monohydrate USP/NF

Microcrystalline Cellulose (PH 102) BP

Stearic Acid BP

Purified Talc BP

1.6.1.6.2 Incompatibilities Not applicable.

1.6.1.6.3 Shelf Life

36 months

1.6.1.6.4 Special Precautions for Storage

Store below 30°C. Protect from light.

1.6.1.6.5 Nature and Contents of Container

10 Tablets are packed in Alu-PVC Blister Pack. Such 10 Blisters are packed in printed Carton with Packing Insert.

1.6.1.6.6 Special precaution for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements.

1.6.1.7 Marketing Authorization Holder And Manufacturing Site Addresses

1.6.1.7.1 Name and Address of Marketing Authorization Holder

Lincoln Pharmaceuticals Limited

Trimul Estate, Khatraj, Taluka: Kalol,

District: Gandhinagar Gujarat, India.

Telephone no.: +91-79-41078096

Fax: +91-79-41078062

Email: hiren@lincolnpharma.com

Website: www.lincolnpharma.com

1.6.1.7.2 Name and Address of manufacturing site(s)

Lincoln Pharmaceuticals Limited
Trimul Estate, Khatraj, Taluka: Kalol,
District: Gandhinagar Gujarat, India.
Telephone no.: +91-79-41078096
Fax: +91-79-41078062
Email: hiren@lincolnpharma.com
Website: www.lincolnpharma.com

1.6.1.8 Marketing Authorization Number

To be included after obtaining first registration.

1.6.1.9 Date of First <Registration> / Renewal of The <Registration> It will be applicable after registration of this product.

1.6.1.10 Date of Revision of the Text

1.6.1.11 Dosimetry (If Applicable)

Not Applicable

1.6.1.12 Instructions for preparation of radiopharmaceuticals (if Applicable)

Not Applicable