## 1.3 Product Information

### 1.3.1 Summary of Product Characteristic (SmPC)

**1. Name of the medicinal product**
**LISINORPIL TABLETS 10 MG**
(Lisinorpil Tablets USP 10 mg)

**2. Qualitative and Quantitative Composition**
**2.1 Label Claim**

Each uncoated tablet contains:
Lisinopril USP
Equivalent to Anhydrous lisinorpil……..10 mg
Excipients…….……...q.s. Colour:
Approved colours used

**2.2 Quantitative Composition**

| Sr. No. | Ingredient Description | Label Claim | Spec. | Function | Quantity/ Tablet (mg) |
|---|---|---|---|---|---|
| 01 | Lisinopril Equivalent to Anhydrous Lisinopril | 5mg | USP | Active | 5.44 |
| 02 | Calcium Hydrogen Phosphate | --- | BP | Diluent/Binder | 42.00 |
| 03 | Pregelatinised Starch | --- | BP | Diluent/Binder | 27.00 |
| 04 | Microcrystalline Cellulose pH 102 | --- | BP | Diluent | 89.26 |
| 05 | Iron oxide Red | --- | IH | Colourant | 0.30 |
| 06 | Croscarmellose Sodium | --- | BP | Disintegrating Agent | 10.00 |
| LUBRICANTS | | | | | |
| 07 | Magnesium Stearate | --- | BP | Lubricant | 6.00 |
| | **Average weight of uncoated tablet = 180 mg ± 7.5 %** | | | | |

Batch Size: 1.0 Lac

**3. Pharmaceutical Form**
Red coloured, round shaped, biconvex, uncoated tablets plain on both sides of each tablet.

## 4. Clinical particulars

### 4.1 Therapeutic indications

**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 digitalis. Acute Myocardial Infarction Lisinopril is indicated for the treatment of hemodynamically stable patients within 24 hours of acute myocardial infarction, to improve survival. Patients should receive, as appropriate, the standard recommended treatments such as thrombolytics, 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.

In considering the use of Lisinopril, it 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

### 4.2 Dosage

Initial Therapy in adults: The recommended 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. Doses up to 80 mg have been used but do not appear to give greater effect. Use with diuretics in adults If blood pressure is not controlled with Lisinopril alone, a low dose of a diuretic may be added (eg, hydrochlorothiazide, 12.5 mg). After the addition of a diuretic, it may be possible to reduce the dose of Lisinopril . The recommended starting dose in adult patients with hypertension taking diuretics is 5 mg once per day. Pediatric Patients 6 years of age and older with hypertension For pediatric patients with glomerular filtration rate > 30 mL/min/1.73m2 , the recommended starting dose is 0.07 mg per kg once daily (up to 5 mg total). Dosage should be adjusted according to blood pressure response up to a maximum of 0.61 mg per kg (up to 40 mg) once daily. Doses above 0.61 mg per kg (or in excess of 40 mg) have not been studied in pediatric patients

Lisinopril is not recommended in pediatric patients < 6 years or in pediatric patients with glomerular filtration rate < 30 mL/min/1.73m2

***Heart Failure***

The recommended starting dose for Lisinopril , when used with diuretics and (usually) digitalis as adjunctive therapy for systolic heart failure, is 10 mg once daily. The recommended starting dose in these patients with hyponatremia (serum sodium < 130 mEq/L) is 2.5 mg once daily. Increase as tolerated to a maximum of 40 mg once daily. Diuretic dose may need to be adjusted to help minimize hypovolemia, which may contribute to hypotension The appearance of hypotension after the initial dose of Lisinopril does not preclude subsequent careful dose titration with the drug,

following effective management of the hypotension.

***Reduction of Mortality in Acute Myocardial Infarction*** In hemodynamically stable patients within 24 hours of the onset of symptoms of acute myocardial infarction, give Lisinopril 10 mg orally, followed by 10 mg after 24 hours, 10 mg after 48 hours and then 10 mg once daily. Dosing should continue for at least six weeks. Initiate therapy with 2.5 mg in patients with a low systolic blood pressure (≤ 120 mmHg and > 100 mm Hg) during the first 3 days after the infarct If hypotension occurs (systolic blood pressure ≤ 100 mmHg) a daily maintenance dose of 10 mg may be given with temporary reductions to 2.5 mg if needed. If prolonged hypotension occurs (systolic blood pressure < 90 mmHg for more than 1 hour) Lisinopril should be withdrawn

***Dose in Patients with Renal Impairment***

No dose adjustment of Lisinopril is required in patients with creatinine clearance > 30 mL/min. In patients with creatinine clearance ≥ 10 mL/min and ≤ 30 mL/min, reduce the initial dose of Lisinopril to half of the usual recommended dose i.e., hypertension, 10 mg; systolic heart failure, 2.5 mg and acute MI, 2.5 mg. Up titrate as tolerated to a maximum of 40 mg daily. For patients on hemodialysis or creatinine clearance < 10 mL/min, the recommended initial dose is 2.5 mg once daily

**4.3 Contraindications**

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.

**4.4 Special warnings and precautions for use**

***Angioedema and Anaphylactoid Reactions*** Angioedema Head and Neck Angioedema Angioedema of the face, extremities, lips, tongue, glottis and/or larynx, including some fatal reactions, have occurred in patients treated with angiotensin converting enzyme inhibitors, including Lisinopril , at any time during treatment. Patients with involvement of the tongue, glottis or larynx are likely to experience airway obstruction, especially those with a history of airway surgery. Lisinopril should be promptly discontinued and appropriate therapy and monitoring should be provided until complete and sustained resolution of signs and symptoms of angioedema has occurred. Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor. ACE inhibitors have been associated with a higher rate of angioedema in black than in non-black patients. Intestinal Angioedema Intestinal angioedema has occurred in patients treated with ACE inhibitors. 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. In some cases, the angioedema was diagnosed by procedures including abdominal CT scan or ultrasound, or at surgery, and symptoms resolved after stopping the ACE inhibitor. Anaphylactoid Reactions Anaphylactoid Reactions During Desensitization Two patients undergoing desensitizing treatment with hymenoptera venom while receiving ACE inhibitors sustained life-threatening anaphylactoid reactions. Anaphylactoid Reactions During Dialysis Sudden and potentially

life threatening anaphylactoid reactions have occurred in some patients dialyzed with high-flux membranes and treated concomitantly with an ACE inhibitor. In such patients, dialysis must be stopped immediately, and aggressive therapy for anaphylactoid reactions must be 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.

***Impaired Renal*** Function Monitor renal function periodically in patients treated with Lisinopril . Changes in renal function including acute renal failure can be caused by drugs that inhibit the renin-angiotensin system. Patients whose renal function may depend in part on the activity of the renin-angiotensin system (eg, patients with renal artery stenosis, chronic kidney disease, severe congestive heart failure, post-myocardial infarction or volume depletion) may be at particular risk of developing acute renal failure on Lisinopril. Consider withholding or discontinuing therapy in patients who develop a clinically significant decrease in renal function on Lisinopril.

***Hypotension*** Lisinopril can cause symptomatic hypotension, sometimes complicated by oliguria, progressive azotemia, acute renal failure or death. Patients at risk of excessive hypotension include those with the following conditions or characteristics: heart failure with systolic blood pressure below 100 mmHg, ischemic heart disease, cerebrovascular disease, hyponatremia, high dose diuretic therapy, renal dialysis, or severe volume and/or salt depletion of any etiology.

In these patients, Lisinopril should be started under very close medical supervision and such patients should be followed closely for the first two weeks of treatment and whenever the dose of Lisinopril and/or diuretic is increased. Avoid use of Lisinopril in patients who are hemodynamically unstable after acute MI. Symptomatic hypotension is also possible in patients with severe aortic stenosis or hypertrophic cardiomyopathy. 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.

***Hyperkalemia*** Serum potassium should be monitored periodically in patients receiving Lisinopril . Drugs that inhibit the renin angiotensin system can cause hyperkalemia. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements and/or potassium-containing salt substitutes.

***Hepatic Failure*** ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice or hepatitis and progresses to fulminant hepatic necrosis and sometimes 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 treatment.

**4.5 Interaction with other medicinal products and other forms of interaction**

Diuretics Initiation of Lisinopril in patients on diuretics may result in excessive reduction of blood pressure. The possibility of hypotensive effects with Lisinopril can be minimized by either

decreasing or discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with Lisinopril . If this is not possible, reduce the starting dose of Lisinopril. Lisinopril attenuates potassium loss caused by thiazide-type diuretics. Potassium-sparing diuretics (spironolactone, amiloride, triamterene, and others) can increase the risk of hyperkalemia. Therefore, if concomitant use of such agents is indicated, monitor the patient's serum potassium frequently. 7.2 Antidiabetics Concomitant administration of Lisinopril and antidiabetic medicines (insulins, oral hypoglycemic agents) may cause an increased blood-glucose-lowering effect with risk of hypoglycemia. 7.3 Non-Steroidal Anti-Inflammatory Agents Including Selective Cyclooxygenase-2 Inhibitors (COX-2 Inhibitors) In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, coadministration of NSAIDs, including selective COX-2 inhibitors, with ACE inhibitors, including lisinopril, may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible. Monitor renal function periodically in patients receiving lisinopril and NSAID therapy.

Avoid use of aliskiren with Lisinopril in patients with renal impairment

**4.6 Fertility, pregnancy and lactation**

***Pregnancy***

Pregnancy Category D Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Resulting oligohydramnios can be associated with fetal lung hypoplasia and skeletal deformations. Potential neonatal adverse effects include skull hypoplasia, anuria, hypotension, renal failure, and death. When pregnancy is detected, discontinue Lisinopril as soon as possible. These adverse outcomes are usually associated with use of these drugs in the second and third trimester of pregnancy. Most epidemiologic studies examining fetal abnormalities after exposure to antihypertensive use in the first trimester have not distinguished drugs affecting the renin-angiotensin system from other antihypertensive agents. Appropriate management of maternal hypertension during pregnancy is important to optimize outcomes for both mother and fetus. In the unusual case that there is no appropriate alternative to therapy with drugs affecting the renin-angiotensin system for a particular patient, apprise the mother of the potential risk to the fetus. Perform serial ultrasound examinations to assess the intra-amniotic environment. If oligohydramnios is observed, discontinue Lisinopril , unless it is considered lifesaving for the mother. Fetal testing may be appropriate, based on the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury. Closely observe infants with histories of in utero exposure to Lisinopril for hypotension, oliguria, and hyperkalemia.

***Breastfeeding***

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 inhibitors, a decision should be made whether to discontinue nursing or discontinue Lisinopril, taking into account the importance of the drug to the mother.

**4.7 Effects on ability to drive and use machines**

Lisinopril can cause blurred vision and make some people feel dizzy or tired, especially when you first start taking it or after an increase in dose. If this happens to you, do not drive a car, ride a bike, or use tools or machinery.

**4.8 Undesirable effects**

In clinical trials in patients with hypertension treated with Lisinopril , 5.7% of patients on Lisinopril discontinued with adverse reactions. The following adverse reactions (events 2% greater on Lisinopril than on placebo) were observed with Lisinopril alone: headache (by 3.8%), dizziness (by 3.5%), cough (by 2.5%). Heart Failure In patients with systolic heart failure treated with Lisinopril for up to four years, 11% discontinued therapy with adverse reactions. 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 adverse reactions (events 2% greater on Lisinopril than on placebo) were observed with Lisinopril : hypotension (by 3.8%), chest pain (by 2.1%). In the two-dose ATLAS trial in heart failure patients, withdrawals due to adverse reactions were not different between the low and high groups, either in total number of discontinuation (17-18%) or in rare specific reactions (< 1%). The following adverse reactions, mostly related to ACE inhibition, were reported more commonly in the high dose group:

**Dose-related Adverse Drug Reactions: ATLAS trial**

| | **High Dose (n=1568)** | **Low Dose (n=1596)** |
|---|---|---|
| Dizziness | 19% | 12% |
| Hypotension | 11% | 7% |
| Creatinine increased 10% 7% | 10% | 7% |
| Hyperkalemia | 6% | 4% |
| Syncope | 7% | 10% |

Acute Myocardial Infarction Patients treated with Lisinopril had a higher incidence of hypotension (by 5.3%) and renal dysfunction (by 1.3%) compared with patients not taking Lisinopril . Other clinical adverse reactions occurring in 1% or higher of patients with hypertension or heart failure treated with Lisinopril in controlled clinical trials and do not appear in other sections of labeling are listed below: Body as a whole: Fatigue, asthenia, orthostatic effects.

***Digestive:*** Pancreatitis, constipation, flatulence, dry mouth, diarrhea. Hematologic: Rare cases of bone marrow depression, hemolytic anemia, leukopenia/neutropenia and thrombocytopenia. Endocrine: Diabetes mellitus, inappropriate antidiuretic hormone secretion.

***Metabolic:*** Gout. Skin: Urticaria, alopecia, photosensitivity, erythema, flushing, diaphoresis, cutaneous pseudolymphoma, toxic epidermal necrolysis, Stevens - Johnson syndrome, and pruritus. Special Senses: Visual loss, diplopia, blurred vision, tinnitus, photophobia, taste disturbances, olfactory disturbance. Urogenital: Impotence. Miscellaneous: A symptom complex has been reported which may include a positive ANA, an elevated erythrocyte sedimentation rate, arthralgia/arthritis, myalgia, fever, vasculitis, eosinophilia, leukocytosis, paresthesia and vertigo. Rash, photosensitivity or other dermatological manifestations may occur alone or in combination with these symptoms.

Clinical Laboratory Test Findings Serum Potassium: In clinical trials hyperkalemia (serum potassium

greater than 5.7 mEq/L) occurred in 2.2% and 4.8% of Lisinopril -treated patients with hypertension and heart failure, respectively. Creatinine, Blood Urea Nitrogen: Minor increases in blood urea nitrogen and serum creatinine, reversible upon discontinuation of therapy, were observed in about 2% of patients with 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 11.6% of patients with heart failure on concomitant diuretic therapy. Frequently, these abnormalities resolved when the dosage of the diuretic was decreased.

Patients with acute myocardial infarction in the GISSI-3 trial treated with Lisinopril had a higher (2.4% versus 1.1% in placebo) incidence of renal dysfunction in-hospital and at six weeks (increasing creatinine concentration to over 3 mg/dL or a doubling or more of the baseline serum creatinine concentration). 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 Lisinopril 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.

**4.9 Overdose**

Following a single oral dose of 20 g/kg no lethality occurred in rats, and death occurred in one of 20 mice receiving the same dose. The most likely manifestation of overdosage would be hypotension, for which the usual treatment would be intravenous infusion of normal saline solution. Lisinopril can be removed by hemodialysis.

**4.10 Pharmacodynamic Effects**

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. 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. 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 pretreatment levels.

***Non-Steroidal Anti-Inflammatory Agents***

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.

**4.11 Pharmacokinetic Properties**

***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. Food does not alter the bioavailability of Lisinopril . 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. Upon multiple dosing, Lisinopril exhibits an effective half-life of 12 hours. 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 urinary recovery, the mean extent of absorption of Lisinopril is approximately 25%, with large intersubject variability (6-60%) at all doses tested (10-80 mg). 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 healthy volunteers. 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 levels increase, time to peak concentration increases and time to attain steady state is prolonged. Lisinopril can be removed by hemodialysis.

***Pediatric Patients***: The pharmacokinetics of Lisinopril were 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 per kg, steady state peak plasma concentrations of 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.

**4.13 Pharmaceutical Particulars:**

**List of Excipients:**

1. Calcium Hydrogen Phosphate
2. Pregelatinised Starch
3. Microcystalline Cellulose pH 102
4. Iron Oxide Red
5. Croscarmellose Sodium
6. Magnesium Stearate

**4.14 Incompatibilities**

Not Applicable

**4.15 Shelf life**

36 Months.

**4.16 Special precautions for disposal and other handling**

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

**4.17 Nature and contents of container**

1 x 10 Tablets packed in Alu-Alu Blister

**Manufactured By:**
**Hab Pharmaceuticals & Research Ltd.,**
10, Pharmacity, Selaqui,
Dehradun, Uttarakhand - 248011,
India

**Marketing authorization holder**
**Hab Pharmaceuticals & Research Ltd.,**
10, Pharmacity, Selaqui,
Dehradun, Uttarakhand – 248011
India