LISINOPRIL TABLET USP 10 MG

SUMMARY OF PRODUCT CHARACTERISTICS (SMPC)

1- Name of the Medicinal Product:

1.1 Product Name

- **Generic Name or International Non-Proprietary Name (INN)**

  Lisinopril Tablet USP 10 mg

1.2 Dosage Strength

Each uncoated tablet contains:
Lisinopril Dihydrate USP
Eq. to Anhydrous Lisinopril .....10 mg
Excipients…….q.s.

1.3 Dosage Form

Uncoated Tablets

2- Quality and Quantitative Composition:

2.1 Qualitative Declaration

Each uncoated tablet contains:
Lisinopril Dihydrate USP
Eq. to Anhydrous Lisinopril .....10 mg
Excipients…….q.s.

2.2 Quantitative Declaration

Description: White colour, Oval shape, uncoated tablet having breakline on one side and plain on other side.

LISINOPRIL TABLET USP 10 MG

STD Batch Size: 90.000 kg / 5.00 Lac Tablets

Sr. No	Ingredients	A.R No.	Specification	Label Claim	Quantity/ Tablet in mg	Standard Qty in kg
Mixing						
1	Maize Starch	RM190360	BP	Nil	45.100	22.550
2	Microcrystalline Cellulose	RM190255	BP	Nil	82.350	41.175
3	Colloidal Silicon Dioxide	RM190305	BP	Nil	2.500	1.250
4	Crosscarmellose Sodium	RM190358	USP	Nil	5.000	2.500
Paste Preparation						
5	PVP K-30	RM190040	USP	Nil	8.000	4.000
6	Purified Water	W190410	BP	Nil	Q.S.	Q.S.
Lubrication						
7	Lisinopril	RM190357	USP	Nil	11.050	5.525
8	Talcum	RM190355	BP	Nil	3.000	1.500
9	Magnesium Stearate	RM193280	BP	Nil	2.500	1.250
10	Crosscarmellose Sodium	RM190358	USP	Nil	6.000	3.000
11	Colloidal Silicon Dioxide	RM190305	BP	Nil	3.500	1.750
12	Sodium Starch Glycolate	RM1903580	BP	Nil	11.000	5.500
Average wt. of Tablet (180.000 mg ± 7.5 %)						

Note:

Active material was calculated on assay or Potency Basis.

IH = In-house Specification

BP = British Pharmacopoeia

USP = United States Pharmacopoeia

Reference. MFR No: MFR/T-E316, Version No: 00

LISINOPRIL TABLET USP 10 MG

1. ***Quantity Adjusted to 100 % API assay***

Calculation:

*Quantity of Lisinopril Dihydrate USP to be dispensed on 100% assay on as is basis.

Lisinopril Dihydrate USP Assay Claimed as 100% Please refer attached Raw Material COA.

3- Pharmaceutical Form:

White colour, Oval shape, uncoated tablet having breakline on one side and plain on other side.

4. Clinical particulars

4.1 Therapeutic indications

Hypertension

Treatment of hypertension.

Heart Failure

Treatment of symptomatic heart failure.

Acute Myocardial Infarction

Short-term (6 weeks) treatment of haemodynamically stable patients within 24 hours of an acute myocardial infarction.

Renal Complications of Diabetes Mellitus

Treatment of renal disease in hypertensive patients with Type 2 diabetes mellitus and incipient nephropathy.

Lisinopril can be used alone or in combination with other antihypertensive agents

4.2 Posology and method of administration

Posology

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

4.3 Contraindications

Hypersensitivity to Lisinopril tablets, to any of the excipients listed in or any other angiotensin converting enzyme (ACE) inhibitor.

• History of angioedema associated with previous ACE inhibitor therapy

• Hereditary or idiopathic angioedema

• Second and third trimesters of pregnancy.

• In combination with aliskiren-containing medicines in patients with diabetes mellitus (type I or

II) or with moderate to severe renal impairment (GFR < 60 ml/min/1.73m^2

4.4 Special warnings and precautions for use

Symptomatic hypotension is seen rarely in uncomplicated hypertensive patients. In hypertensive patients receiving Lisinopril tablets, hypotension is more likely to occur if the patient has been volume-depleted e.g. by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting, or has severe renin-dependent hypertension. In patients with heart failure, with or without associated renal insufficiency, symptomatic hypotension has been observed. This is most likely to occur in those patients with more severe degrees of heart failure, as reflected by the use of high doses of loop diuretics, hyponatraemia or functional renal impairment. In patients at increased risk of symptomatic hypotension, initiation of therapy and dose adjustment should be closely monitored. Similar considerations apply to patients with ischaemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

If hypotension occurs, the patient should be placed in the supine position and, if necessary, should receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses, which can be given usually without difficulty once the blood pressure has increased after volume expansion.

In some patients with heart failure who have normal or low blood pressure, additional lowering of systemic blood pressure may occur with Lisinopril tablets. This effect is anticipated and is not usually a reason to discontinue treatment. If hypotension becomes symptomatic, a reduction of dose or discontinuation of Lisinopril tablets may be necessary.

Hypotension In Acute Myocardial Infarction

Treatment with Lisinopril tablets must not be initiated in acute myocardial infarction patients whoare 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.

Aortic and mitral valve stenosis / hypertrophic cardiomyopathy

As with other ACE inhibitors, Lisinopril tablets 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 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.

Anaphylactoid reactions in Haemodialysis Patients

Anaphylactoid reactions have been reported in patients dialysed with high flux membranes (e.g. AN 69) and treated concomitantly with an ACE inhibitor. In these patients consideration should be given to using a different type of dialysis membrane or different class of antihypertensive agent.

Anaphylactoid reactions during low-density lipoproteins (LDL) apheresis

Rarely, patients receiving ACE inhibitors during low-density lipoproteins (LDL) apheresis with dextran sulphate have experienced life-threatening anaphylactoid reactions. 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. In the same patients, these reactions have been avoided when

ACE inhibitors were temporarily withheld but they have reappeared upon inadvertent readministration of the medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

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 RAASacting 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.

4.6 Fertility, pregnancy and lactation

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. 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. Exposure to ACE inhibitor therapy during the second and third trimesters is known to induce human foetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia). Should exposure to ACE inhibitor have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended. Infants whose mothers have taken ACE inhibitors should be closely observed for hypotension.

Breast-feeding

Because no information is available regarding the use of Lisinopril tablet during breastfeeding,

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

4.7 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.

4.8 Undesirable effects

The following undesirable effects have been observed and reported during treatment with

Lisinopril tablets 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

Blood and the lymphatic system disorders:

rare: decreases in haemoglobin, decreases in haematocrit.

very rare: bone marrow depression, anaemia, thrombocytopenia, leucopenia, neutropenia,

agranulocytosis, 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

Nervous system and psychiatric disorders:

common: dizziness, headache

uncommon: mood alterations, paraesthesia, vertigo, taste disturbance, sleep disturbances, hallucinations.

rare: mental confusion, olfactory disturbance

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: hypersensitivity/angioneurotic oedema: angioneurotic oedema of the face, extremities, lips, tongue, glottis, and/or larynx, urticaria, alopecia, psoriasis

very rare: sweating, pemphigus, toxic epidermal necrolysis, Stevens-Johnson Syndrome, erythema

multiforme, cutaneous pseudolymphoma

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 Pharmacodynamic properties

Pharmacotherapeutic group: Angiotensin converting enzyme inhibitors,

ATC code: C09A A03.

Mechanism of action

Lisinopril tablets 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

Whilst 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.

5.2 Pharmacokinetic properties

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 inter-patient variability of 6-60% over the dose range studied (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 be bound to 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 is excreted entirely unchanged into 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. In mild to moderate renal impairment (creatinine clearance 30-80 ml/min) mean AUC was increased by 13% only, while a 4.5-fold increase in mean AUC was observed in severe renal impairment (creatinine clearance 5-30 ml/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.

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

- Maize Starch
- Microcrystalline cellulose Powder
- Colloidal Silicon Dioxide
- Crosscarmellose Sodium
- PVP K-30
- Purified Water
- Talcum
- Magnesium Stearate
- Sodium Starch Glycolate

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 Years from the date of manufacture.

6.4 Special precautions for storage

Store below 30°C.

Protect from light and moisture.

6.5 Nature and contents of container

a. Pack 14 Tablets in a Blister with the help of Printed Alu foil and clear PVC foil in the in the arrangement of 1 x 14's. Such 2 blisters are packed in a carton along with a pack insert in the arrangement of 2 x 14's.

b. 3 x 10 Tablets per pack.

6.6 Special precautions for disposal <and other handling>

No special requirements

7- Manufacturer Name:

SURMOUNT LABORATORIES PVT. LTD.
Plot No A-2/4003, GIDC Ind. Estate,
Ankleshwar-393002, Gujarat, India
Email: surmountlaborat@gmail.com

8.0 Marketing authorization number (s)

To be allocated

9.0 Date of first authorization / renewal of authorization

To be allocated

10.0 Date of revision of the text

To be allocated