1. Name of the drug product:

LISINOPRIL TABLETS USP 10 MG

2 Qualitative and quantitative composition:
Each Uncoated Tablet Contains:
Lisinopril Dihydrate Equivalent to Lisinopril (Anhydrous) USP 10 mg
Excipients Q.S.
Approved Colour Used.

Sr. No.	Ingredients	Specifi-cation	Label Claim / Tablet (In mg)	Over-ages added (In %)	Qty. / Tablet (In mg)	Reason for Inclusion
a)	**Dry Mixing**					
1.	Lisinopril Dihydrate	USP	Lisinopril Dihydrate Equivalent to Lisinopril (Anhydrous) 10mg	NA	10.90	Medicament
2.	Lactose Monohydrate	BP	NA	NA	89.00	Diluent
3.	Maize Starch	BP	NA	NA	66.10	Binder
b)	**Binder Preparation**					
4.	Povidone K-30	BP	NA	NA	8.00	Binder
5.	Purified Water	BP	NA	NA	----	Vehicle
c)	**Lubrication**					
6.	Purified Talc	BP	NA	NA	3.93	Glidant
7.	Magnesium Stearate	BP	NA	NA	2.00	Lubricant
8.	Titanium Dioxide	BP	NA	NA	0.07	Colour
	Average weight of uncoated tablet (In mg)				**180.00**	

3 Pharmaceutical form: Uncoated tablets
Description: White, oval shaped, biconvex uncoated tablet, having embossing L10 and groove line on one side, plain on other side.

4 Clinical Particulars
4.1 Therapeutic indications
LISINOPRIL TABLETS USP 10 MG is indicated in:

- Treatment of hypertension.
- Treatment of symptomatic heart failure.
- Short-term 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.

4.2 Posology and method of administration
Route: Oral
DOSAGE FOR HYPERTENSION
Adult dosage (ages 18–64 years)
- Starting dose: 5 mg taken by mouth once per day
- Usual dose: 20–40 mg taken once per day
- Maximum dose: 80 mg taken once per day

Child dosage (ages 6–17 years)
- Starting dose: 0.07 mg/kg of body weight taken by mouth once per day
- Dose adjustments will be based on blood pressure response.
- Maximum dose: 0.61 mg/kg, up to 40 mg, once per day

DOSAGE FOR HEART FAILURE
Adult dosage (ages 18–64 years)
- Starting dose: 5 mg taken by mouth once per day
- Maximum dose: 40 mg taken once per day

Child dosage (ages 0–17 years)
This medicine should not be used in children younger than 18 years for heart failure.

DOSAGE FOR ACUTE MYOCARDIAL INFARCTION (HEART ATTACK)
Adult dosage (ages 18–64 years)
- Starting dose: 5 mg taken by mouth within the first 24 hours of when symptoms of heart attack start. Doctor will give you another 5 mg after another 24 hours.
- Usual dose: 10 mg given 48 hours after heart attack. Then 10 mg taken once per day for at least 6 weeks.

Child dosage (ages 6–17 years)
This medicine should not be used in children younger than 18 years for improving survival after a heart attack.

4.3 Contraindications
LISINOPRIL TABLETS USP 10 MG are contraindicated in:
- Patients with hypersensitivity to Lisinopril and any other excipients used in the formulation.
- 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
Talk to your physician or pharmacist before taking **LISINOPRIL TABLETS USP 10 MG** if you:
- Are dehydrated due to sickness and diarrhoea, use of diuretics (water tablets), on a low salt diet or have severe renin-dependent hypertension.
- Have reduced blood flow to the heart (ischaemic heart disease) or disease of the blood vessels in the brain (cerebrovascular disease).
- Have any of the following heart diseases: heart failure, narrowing (stenosis) of the opening of the aortic or mitral valve or enlarged heart (hypertrophic cardiomyopathy).
- Had a heart attack and have low blood pressure or are in cardiogenic shock.

- Have reduced kidney function, narrowing of the arteries supplying the kidneys or renovascular hypertension (high blood pressure due to a blockage in a blood vessel in the kidney).
- Are having dialysis or have a kidney transplant.
- Are receiving treatment to lessen your reactions to bee or wasp stings or for so called LDL apheresis.
- Have had surgery on your airways.
- Have problems with your immune system due to some illness or medicines such as scleroderma, lupus erythematosus, allopurinol, procainamide or drugs to suppress the immune system (especially if you also have impaired kidney function).
- Have diabetes.
- Are taking any of the following medicines used to treat high blood pressure:
  1. An angiotensin II receptor blocker (ARBs) (also known as sartans – for example valsartan, telmisartan, irbesartan), in particular if you have diabetes-related kidney problems.
  2. Aliskiren
- if you are taking any of the following medicines, the risk of angioedema (rapid swelling under the skin in area such as the throat) is increased: Sirolimus, everolimus and other medicines belonging to the class of mTOR inhibitors (used to avoid rejection of transplanted organs).

4.5 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.

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.

Diuretics

When a diuretic is added to the therapy of a patient receiving Lisinopril 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 is added. The possibility of symptomatic hypotension with Lisinopril can be minimised by discontinuing the diuretic prior to initiation of treatment with Lisinopril.

Potassium supplements, potassium-sparing diuretics or potassium-containing salt substitutesand 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 potassiumlosing diuretic, diuretic induced hypokalaemia may be ameliorated.

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 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.

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.

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.

Sympathomimetics

Sympathomimetics may reduce the antihypertensive effects of ACE inhibitors.

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.

Tissue Plasminogen Activators

Concomitant treatment with tissue plasminogen activators may increase the risk of angioedema.

Acetylsalicylic acid, thrombolytics, beta-blockers, nitrates

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

4.6 Pregnancy and Lactation

Pregnancy

The use of Lisinopril is not recommended during the first trimester of pregnancy. The use of Lisinopril is contraindicated during the second and third trimester of pregnancy.

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.

Lactation

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

4.7 Effects on ability to drive and use machines
Lisinopril may affect your ability to drive or use machines. If the tablets make you feel sick, dizzy or tired, or give you a headache, do not drive or use machines and contact your doctor immediately.

4.8 Undesirable effects
More common side effects
Headache, Dizziness, Persistent cough, Low blood pressure, Chest pain

Serious side effects
Hypersensitivity (allergic) reaction. Symptoms include:
Swelling on face, lips, tongue, or throat; Trouble breathing, Trouble swallowing, Stomach (abdomen) pain with or without nausea or vomiting

Kidney problems. Symptoms include:
Tiredness swelling, especially on hands, feet, or ankles; Shortness of breath; Weight gain.

Liver failure. Symptoms include:
Yellowing of skin and the whites of eyes, Elevated liver enzymes, Stomach pain, Nausea and Vomiting, High potassium levels.

4.9 Overdose
Symptoms
Symptoms of Lisinopril Tablets overdose include hypotension, circulatory shock, electrolyte disturbances, renal failure, hyperventilation, tachycardia, palpitations, bradycardia, dizziness, anxiety and cough.
Treatment
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 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.

5.2 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 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.

Elderly

Older patients have higher blood levels and higher values for the area under the plasma concentration time curve (increased approximately 60%) compared with younger subjects.

Paediatrics

The pharmacokinetic profile of lisinopril was studied in 29 paediatric hypertensive patients, aged between 6 and 16 years, with a GFR above 30 ml/min/1.73m^2. After doses of 0.1 to 0.2 mg/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.

AUC and C_{max} values in children in this study were consistent with those observed in adults.

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

Lactose Monohydrate, Maize starch, Povidone K-30, Purified Water, Purified talc, Magnesium stearate, Titanium Dioxide

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store below 30°C in a dry & dark place.
Keep all medicines out of the reach of children.
Read leaflet carefully before use.

1.3.1.6.5 Nature and contents of container

Packing:

Primary packing: 14 Tablets in an ALU-PVC blister.
Secondary packing: 2 Blisters are packed in a carton along with leaflet.
Tertiary packing: Shrink such 10 cartons. Such 20 Shrinks are packed in a 5 Ply corrugated box sealed with BOPP tape & strap with strapping roll.

1.3.1.7 Applicant / Manufacturer

Applicant

Applicant name and address	**M/s. IBU PHARMA NIGERIA LIMITED.** 1,Labiran Street, Ikenne, Ogun State
Contact person's phone number	
Contact person's email	

Manufacturer

Manufacturer name and address	**M/s. IMPULSE PHARMA PVT. LTD.** J-201, J-202/1 , MIDC Tarapur, Boisar, Dist. Palghar - 401506, Maharashtra State, India.
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