# AMLOPRES-L Tablets (Amlodipine + Lisinopril)

## Qualitative and Quantitative Composition

**Amlopres-L**
Each tablet contains:

Amlodipine besylate equivalent to amlodipine ……5 mg

Lisinopril (Anhydrous)……5 mg

## Dosage Form and Strength

Oral tablet

Amlodipine 5mg and Lisinopril 5mg

## Clinical Particulars

### Therapeutic Indications

**AMLOPRES-L** is indicated in the treatment of mild to moderate hypertension.

### Posology and Method of Administration

The usual initial dosage is one tablet daily. If blood pressure control is inadequate after a week or two, the dose may be increased to two tablets daily. The dosage, however, should be individualized.

### Contraindications

Hypersensitivity to either component

History of angioedema related to previous treatment with an ACE inhibitor patients with hereditary or idiopathic angioedema

Second and third trimesters of pregnancy

Concomitant use of Lisinopril with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m2)

Severe hypotension

Shock (including cardiogenic shock)

Hypersensitivity to dihydropyridine derivatives, amlodipine or any of the excipients.

Hemodynamically unstable heart failure after acute myocardial infarction

Obstruction of the outflow-tract of the left ventricle (e.g. high grade aortic stenosis).

## Special Warnings and Precautions for Use

### *General*

#### ***Angioedema and Anaphylactoid Reactions***

Patients taking concomitant mTOR inhibitor (e.g. temsirolimus, sirolimus, everolimus) therapy may be at increased risk for angioedema.

*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 nonblack 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 scanor 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 lifethreatening 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.

***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 myocardial infarction.

Symptomatic hypotension is also possible in patients with severe aortic stenosis or hypertrophic cardiomyopathy.

Symptomatic hypotension is possible with amlodipine, particularly in patients with severe aortic stenosis. Because of the gradual onset of action, acute hypotension is unlikely.

***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 RAAS can cause hyperkalemia. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics (e.g. spironolactone, triamterene or amiloride), potassium supplements and/or potassium-containing salt substitutes or those patients taking other drugs associated with increases in serum potassium (e.g. heparin, the combination trimethoprim/sulfamethoxazole also known as cotrimoxazole). If concomitant use of the above mentioned agents is deemed appropriate, regular monitoring of serum potassium is recommended.

***Increased Angina and/or Myocardial Infarction***

Worsening angina and acute myocardial infarction can develop after starting or increasing the dose of amlodipine, particularly in patients with severe obstructive coronary artery disease.

***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.

***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. Lisinopril should be used with extreme caution in patients with collagen vascular disease, immunosuppressant therapy, treatment with allopurinol or procainamide, or a combination of these complicating factors, especially if there is preexisting impaired renal function. Some of these patients developed serious infections, which in a few instances did not respond to intensive antibiotic therapy. If Lisinopril is used in such patients, periodic monitoring of white blood cell counts is advised and patients should be instructed to report any sign of infection.

***Cough***

Cough has been reported with the use of ACE inhibitors. Characteristically, the cough is nonproductive, persistent and resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough.

***Race***

ACE inhibitors, including Lisinopril, have an effect on blood pressure that is less in black patients than in non-blacks.

***Fetal Toxicity***

Lisinopril can cause fetal harm when administered to a pregnant woman. Use of drugs that act on the RAAS 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.

***Drug Interactions***

***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.

***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 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, hyperkalemia and decreased renal function (including acute renal failure) compared to the use of a single RAAS acting agent.

***Antidiabetics***

Concomitant administration of ACE inhibitors and antidiabetic medicines (insulins, oral hypoglycemic agents) may cause an increased blood glucose-lowering effect with risk of hypoglycemia.

Dual Blockade of the RAAS: Dual blockade of the RAAS with angiotensin receptor blockers, ACE inhibitors, or aliskiren is. associated with increased risks of hypotension, hyperkalemia, and changes in renal function (including acute renal failure) compared to monotherapy.

The VA NEPHRON trial enrolled 1448 patients with type 2 diabetes, elevated urinary-albumin--o-creatinine ratio, and decreased estimated glomerular filtration rate (GFR 30 to 89.9 ml/min), randomized them to lisinopril or placebo on a background of losartan therapy and followed them for a median of 2.2 years. Patients receiving the combination of losartan and lisinopril did not obtain any additional benefit compared to monotherapy for the combined endpoint of decline in GFR, end state renal disease, or death, but experienced an increased incidence of hyperkalemia and acute kidney injury compared with the monotherapy group.

In general, avoid combined use of RAS inhibitors. Closely monitor blood pressure, renal function and electrolytes inpatients on lisinopril and other agents that affect the RAS.

Do not co-administer aliskiren with lisinopril in patients with diabetes. Avoid use of aliskiren with lisinopril in patients with renal impairment (GFR <60 ml/min).

Lithium: Lithium toxicity has been reported in patients receiving lithium concomitantly with drugs, which cause elimination of sodium, including ACE inhibitors. Lithium toxicity was usually reversible upon discontinuation of lithium and the ACE inhibitor. Monitor serum lithium levels during concurrent use.

Gold: Nitritoid reactions (symptoms include facial flushing, nausea, vomiting and hypotension) have been reported rarely in patients on therapy with injectable gold (sodium aurothiomalate) and concomitant ACE inhibitor therapy including lisinopril.

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs): 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.

The antihypertensive effect of ACE inhibitors, including lisinopril, may be attenuated by NSAIDs.

Tricyclic Antidepressants / Antipsychotics / Anesthetics: Concomitant use of certain anesthetic 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 medicines (insulins, oral hypoglycemic agents) may cause an increased blood glucose-lowering effect with risk of hypoglycemia.

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.

CYP3A4 Inhibitors: Coadministration of a 180 mg daily dose of diltiazem with 5 mg amlodipine in elderly hypertensive patients resulted in a 60% increase in amlodipine systemic exposure. Erythromycin coadministration in healthy volunteers did not significantly change amlodipine systemic exposure. However, strong inhibitors of CYP3A (e.g.,itraconazole, clarithromycin) may increase the plasma concentrations of amlodipine to a greater extent.

CYP3A Inducers: No information is available on the quantitative effects of CYP3A inducers on amlodipine. Blood pressure should be closely monitored when amlodipine is coadministered with CYP3A inducers.

Sildenafil: Monitor for hypotension when sildenafil is coadministered with amlodipine.

Simvastatin: Coadministration of simvastatin with amlodipine increases the systemic exposure of simvastatin. Limit the dose of simvastatin in patients on amlodipine to 20 mg daily. Coadministration of multiple doses of 10 mg of amlodipine with 80 mg simvastatin resulted in a 77% increase in exposure to simvastatin compared to simvastatin alone.

Cyclosporine: A prospective study in renal transplant patients (N=11) showed on an average of 40% increase in trough cyclosporine levels when concomitantly treated with amlodipine.

Tacrolimus: A prospective study in healthy Chinese volunteers (N=9) with CYP3A5 expressers showed a 2.5-to 4-fold increase in tacrolimus exposure when concomitantly administered with amlodipine compared to tacrolimus alone. This finding was not observed in CYP3A5 nonexpressers (N= 6). However, a 3-fold increase in plasma exposure to tacrolimus in a renal transplant patient (CYP3A5 nonexpresser) upon initiation of amlodipine for the treatment of post-transplant hypertension resulting in reduction of tacrolimus dose has been reported. Irrespective of the CYP3A5 genotype status, the possibility of an interaction cannot be excluded with these drugs.

Dantrolene (infusion): In animals, lethal ventricular fibrillation and cardiovascular collapse are observed in association with hyperkalaemia after administration of verapamil and intravenous dantrolene. Due to risk of hyperkalaemia, it is recommended that the coadministration of calcium channel blockers such as amlodipine be avoided in patients susceptible to malignant hyperthermia and in the management of malignant hyperthermia.

***Effects of Amlodipine on Other Medicinal Products***

The blood pressure lowering effects of amlodipine adds to the blood pressure-lowering effects of other medicinal products with antihypertensive properties.

In clinical interaction studies, amlodipine did not affect the pharmacokinetics of atorvastatin, digoxin, warfarin or cyclosporin.

Others: Co-administered cimetidine, magnesium and aluminum hydroxide antacids, sildenafil, and grapefruit juice have no impact on the exposure to amlodipine.

***Use in Special Population***

***Renal Impairment***

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 RAAS. Patients whose renal function may depend in part on the activity of the RAAS (e.g., patients with renal artery stenosis, chronic kidney disease, severe congestive heart failure, postmyocardial 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.

***Hepatic Impairment***

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.

Because amlodipine is extensively metabolized by the liver and the plasma elimination half-life (t1/2) is 56 hours in patients with impaired hepatic function, titrate slowly when administering amlodipine to patients with severe hepatic impairment.

***Pregnancy***

Risk Summary

Lisinopril can cause fetal harm when administered to a pregnant woman. Use of drugs that act on the RAAS during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Most epidemiologic studies examining fetal abnormalities after exposure to antihypertensive use in the first trimester have not distinguished drugs affecting the RAAS from other antihypertensive agents. When pregnancy is detected, discontinue lisinopril as soon as possible.

The estimated background risk of major birth defects and miscarriage for the indicated population(s) are unknown. In the general U.S. population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

Hypertension in pregnancy increases the maternal risk for pre-eclampsia, gestational diabetes, premature delivery, and delivery complications (e.g., need for cesarean section, and post-partum hemorrhage). Hypertension increases the fetal risk for intrauterine growth restriction and intrauterine death. Pregnant women with hypertension should be carefully monitored and managed accordingly.

Fetal/Neonatal Adverse Reactions

Oligohydramnios in pregnant women who use drugs affecting the RAAS in the second and third trimesters of pregnancy can result in the following: reduced fetal renal function leading to anuria and renal failure, fetal lung hypoplasia and skeletal deformations, including skull hypoplasia, hypotension, and death. In the unusual case that there is noappropriate alternative to therapy with drugs affecting the RAAS for a particular patient, apprise the mother of the potential risk to the fetus.

***Lactation***

No data are available regarding the presence of lisinopril in human milk or the effects of lisinopril on the breast fed infant or on milk production. Lisinopril is present in rat milk. Because of the potential for severe adverse reactions in thebreastfed infant, advise women not to breastfeed during treatment with lisinopril. is not known whether amlodipine isexcreted in human milk. In the absence of this information, it is recommended that nursing be discontinued whileamlodipine is administered.

***Pediatric use***

Amlodipine (2.5 to 5 mg daily) is effective in lowering blood pressure in patients 6 to 17 years. Effect of amlodipine on blood pressure in patients less than 6 years of age is not known.

Antihypertensive effects and safety of lisinopril have been established in pediatric patients aged 6 to 16 years. No relevant differences between the adverse reaction profile for pediatric patients and adult patients were identified. Safety and effectiveness of lisinopril have not been established in pediatric patients under the age 6 or in pediatric patients with glomerular filtration rate < 30 mL/min/1.73 $m^2$.

Neonates with a history of in utero exposure to Lisinopril:

If oliguria or hypotension occurs, direct attention toward support of blood pressure and renal perfusion. Exchange transfusions or dialysis may be required as a means of reversing hypotension and/or substituting for disordered renalfunction.

***Geriatric Use***

No dosage adjustment with lisinopril is necessary in elderly patients. In a clinical study of lisinopril in patients with myocardial infarctions (GISSI-3 Trial) 4,413 (47%) were 65 and over, while 1,656 (18%) were 75 and over. In this study, 4.8 % of patients aged 75 years and older discontinued lisinopril treatment because of renal dysfunction vs. 1.3% of patients younger than 75 years. No other differences in safety or effectiveness were observed between elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Clinical studies of amlodipine did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. Elderly patients have decreased clearance of amlodipine with a resulting increase of AUC of approximately 40–60%, and a lower initial dose may be required.

***Effects on the Ability to Drive and Use Machines***

Caution is recommended, especially at the start of treatment with the combination.

## Undesirable Effects

### Amlodipine

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of

another drug and may not reflect the rates observed in practice. Amlodipine has been evaluated for safety in more than 11,000 patients in clinical trials.

In general, treatment with amlodipine was well-tolerated at doses up to 10 mg daily. Most adverse reactions reported during therapy with amlodipine were of mild or moderate severity. In controlled clinical trials directly comparing amlodipine at doses up to 10 mg to placebo, discontinuation of amlodipine due to adverse reactions was required in only about 1.5% of patients and was not significantly different from placebo (about 1%). The most commonly reported side effects more frequent than placebo are reflected in the table 1 below.

***Summary of adverse drug reactions from clinical studies***

| **Adverse Events** | **2.5 mg (N = 275) %** | **5 mg (N = 296) %** | **10 mg (N = 268) %** | **Placebo (N = 520) %** |
|---|---|---|---|---|
| Edema | 1.8 | 3.0 | 10.8 | 0.6 |
| Dizziness | 1.1 | 3.4 | 3.4 | 1.5 |
| Flushing | 0.7 | 1.4 | 2.6 | 0.0 |
| Palpitation | 0.7 | 1.4 | 4.5 | 0.6 |

Other adverse experiences that were not clearly dose-related but were reported with an incidence greater than 1.0% in placebo-controlled clinical trials included the following:

| | **Amlodipine (%) (N = 1,730)** | **Placebo (%) (N = 1,250)** |
|---|---|---|
| Fatigue | 4.5 | 2.8 |
| Nausea | 2.9 | 1.9 |
| Abdominal pain | 1.6 | 0.3 |
| Somnolence | 1.4 | 0.6 |

For several adverse experiences that appear to be drug- and dose-related, there was a greater incidence in women than men associated with amlodipine treatment as shown in the following table:

| **Adverse Event** | **Amlodipine** | | **Placebo** | |
|---|---|---|---|---|
| | **Male (%) (N = 1,218)** | **Female (%) (N = 512)** | **Male (%) (N = 914)** | **Female (%) (N = 336)** |
| Oedema | 5.6 | 14.6 | 1.4 | 5.1 |
| Flushing | 1.5 | 4.5 | 0.3 | 0.9 |
| Palpitations | 1.4 | 3.3 | 0.9 | 0.9 |
| Somnolence | 1.3 | 1.6 | 0.8 | 0.3 |

The following events occurred in <1% but >0.1% of patients in controlled clinical trials or under conditions of open trials or marketing experience where a causal relationship is uncertain; they are

listed to alert the physician to a possible relationship:

*Cardiovascular*: Arrhythmia (including ventricular tachycardia and atrial fibrillation), bradycardia, chest pain, peripheral ischaemia, syncope, tachycardia, vasculitis.

*Central and Peripheral Nervous System*: Hypoesthesia, neuropathy peripheral, paraesthesia, tremor, vertigo.

*Gastrointestinal*: Anorexia, constipation, dysphagia, diarrhoea, flatulence, pancreatitis, vomiting, gingival hypertrophy.

*General*: Allergic reaction, asthenia**, back pain, hot flushes, malaise, pain, rigors, weight gain, weight decrease.

*Musculoskeletal System*: Arthralgia, arthrosis, muscle cramps**, myalgia.

*Psychiatric*: Sexual dysfunction (male** and female), insomnia, nervousness, depression, abnormal dreams, anxiety, depersonalization.

*Respiratory System*: Dyspnoea**, epistaxis.

*Skin and Appendages*: Angio-oedema, erythema multiforme, pruritus, rash, rash erythematous, rash maculopapular.

*Special Senses*: Abnormal vision, conjunctivitis, diplopia, eye pain, tinnitus.

*Urinary System*: Micturition frequency, micturition disorder, nocturia.

*Autonomic Nervous System*: Dry mouth, sweating increased.

*Metabolic and Nutritional*: Hyperglycaemia, thirst.

*Haemopoietic*: Leucopenia, purpura, thrombocytopaenia.

**These events occurred in less than 1% in placebo-controlled trials, but the incidence of these side effects was between 1% and 2% in all multiple-dose studies.

Amlodipine therapy has not been associated with clinically significant changes in routine laboratory tests. No clinically relevant changes were noted in serum potassium, serum glucose, total triglycerides, total cholesterol, HDL cholesterol, uric acid, blood urea nitrogen, or creatinine.

In the CAMELOT and PREVENT studies, the adverse event profile was similar to that reported previously (see above), with the most common adverse event being peripheral oedema.

**Lisinopril**

***Hypertension***

In clinical trials in patients with hypertension treated with Lisinopril, discontinuation of therapy due to clinical adverse experiences occurred in 5.7% of patients. The overall frequency of adverse experiences could not be related to total daily dosage within the recommended therapeutic dosage range.

For adverse experiences occurring in greater than 1% of patients with hypertension treated with

Lisinopril or Lisinopril plus hydrochlorothiazide in controlled clinical trials, and more frequently with Lisinopril and/or Lisinopril plus hydrochlorothiazide than placebo, comparative incidence data are listed in the table below:

| | **Incidence** | **(n=629)** | **Incidence** |
|---|---|---|---|
| | **(discontinuation)** | **Incidence** | **(discontinuation)** |
| Body as a Whole<br>Fatigue<br>Asthenia<br>Orthostatic Effects<br>Cardiovascular | 2.5 (0.3) 1.3 (0.5)<br>1.2 (0.0) | **(discontinuation)**<br>4.0 (0.5)<br>2.1 (0.2)<br>3.5 (0.2) | 1.0 (0.0) 1.0 (0.0)<br>1.0 (0.0) |
| Hypotension<br>Digestive<br>Diarrhea<br>Nausea<br>Vomiting<br>Dyspepsia<br>Musculoskeletal | 1.2 (0.5)<br>2.7 (0.2)<br>2.0 (0.4)<br>1.1 (0.2)<br>0.9 (0.0) | 1.6 (0.5)<br>2.7 (0.3)<br>2.5 (0.2) 1.4 (0.1)<br>1.9 (0.0) | 0.5 (0.5)<br>2.4 (0.0)<br>2.4 (0.0) 0.5 (0.0)<br>0.0 (0.0) |
| Muscle Cramps<br>Nervous/Psychiatric<br>Headache<br>Dizziness<br>Paresthesia<br>Decreased Libido<br>Vertigo<br>Respiratory<br>Cough<br>Upper Respiratory Infection | 0.5 (0.0)<br>5.7 (0.2)<br>5.4 (0.4) 0.8 (0.1)<br>0.4 (0.1) 0.2 (0.1)<br>3.5 (0.7)<br>2.1 (0.1) | 2.9 (0.8)<br>4.5 (0.5)<br>9.2 (1.0) 2.1 (0.2)<br>1.3 (0.1) 1.1 (0.2)<br>4.6 (0.8)<br>2.7 (0.1) | 0.5 (0.0)<br>1.9 (0.0)<br>1.9 (0.0)<br>0.0 (0.0) 0.0 (0.0)<br>0.0 (0.0)<br>1.0 (0.0)<br>0.0 (0.0) |
| Common Cold<br>Nasal Congestion<br>Influenza Skin | 1.1 (0.1) 0.4 (0.1)<br>0.3 (0.1) | 1.3 (0.1)<br>1.3 (0.1)<br>1.1 (0.1) | 0.0 (0.0)<br>0.0 (0.0)<br>0.0 (0.0) |
| Rash<br>Urogenital<br>Impotence | 1.3 (0.4) 1.0 (0.4) | 1.6 (0.2) 1.6 (0.5) | 0.5 (0.5)<br>0.0 (0.0) |

Chest pain and back pain were also seen, but were more common on placebo than Lisinopril.

Heart Failure:

In patients with heart failure treated with Lisinopril for up to four years, discontinuation of therapy due to clinical adverse experiences occurred in 11.0% of patients. 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 table lists those adverse experiences which occurred in greater than 1% of patients with heart failure treated with Lisinopril or placebo for up to 12 weeks in controlled clinical trials, and more frequently on Lisinopril than placebo.

> 1% with Lisinopril but more frequent or as frequent on placebo than Lisinopril in controlled trials

were asthenia, angina pectoris, nausea, dyspnea, cough, and pruritus.

Worsening of heart failure, anorexia, increased salivation, muscle cramps, back pain, myalgia, depression, chest sound abnormalities, and pulmonary edema were also seen in controlled clinical trials, but were more common on placebo than Lisinopril.

| | **Lisinopril** | **Placebo** |
|---|---|---|
| | **(n=407)** | **(n=155)** |
| | **Incidence** | **Incidence** |
| | **(discontinuation)** | **(discontinuation)** |
| Body as a Whole | **12 weeks** | **12 weeks** |
| Chest Pain<br>Abdominal Pain<br>Cardiovascular | 3.4 (0.2)<br>2.2 (0.7) | 1.3 (0.0)<br>1.9 (0.0) |
| Hypotension<br>Digestive<br>Diarrhea<br>Nervous/Psychiatric<br>Dizziness<br>Headache<br>Respiratory<br>Upper Respiratory<br>Infection<br>Skin | <br><br><br>4.4 (1.7) 3.7 (0.5)<br>11.8 (1.2)<br>4.4 (0.2)<br>1.5 (0.0) | <br><br><br>0.6 (0.6) 1.9 (0.0)<br>4.5 (1.3)<br>3.9 (0.0)<br>1.3 (0.0) |
| Rash | 1.7 (0.5) | 0.6 (0.6) |

In the two-dose ATLAS trial in heart failure patients, withdrawals due to adverse events were not different between the low and high groups, either in total number of discontinuation (17-18%) or in rare specific events (<1%). The following adverse events, mostly related to ACE inhibition, were reported more commonly in the high dose group:

| **% of patients** | **High Dose** | **Low dose** |
|---|---|---|
| **Events** | **(N=1568)** | **(N=1596)** |

| | | |
|---|---|---|
| Dizziness | 18.9 | 12.1 |
| Hypotension | 10.8 | 6.7 |
| Creatinine increased | 9.9 | 7.0 |
| Hyperkalemia | 6.4 | 3.5 |

***Acute Myocardial Infarction***

In the GISSI-3 trial, in patients treated with Lisinopril for six weeks following acute myocardial infarction, discontinuation of therapy occurred in 17.6% of patients.

Patients treated with Lisinopril had a significantly higher incidence of hypotension and renal dysfunction compared with patients not taking Lisinopril.

In the GISSI-3 trial, hypotension (9.7%), renal dysfunction (2.0%), cough (0.5%), post infarction angina (0.3%), skin rash and generalized edema (0.01%), and angioedema (0.01%) resulted in withdrawal of treatment. In elderly patients treated with Lisinopril, discontinuation due to renal dysfunction was 4.2%.

Other clinical adverse experiences occurring in 0.3% to 1.0% of patients with hypertension or heart failure treated with Lisinopril in controlled clinical trials and rarer, serious, possibly drug-related events reported in uncontrolled studies or marketing experience are listed below, and within each category are in order of decreasing severity:

Body as a Whole: Anaphylactoid reactions syncope, orthostatic effects, chest discomfort, pain, pelvic pain, flank pain, edema, facial edema, virus infection, fever, chills, malaise.

Cardiovascular: Cardiac arrest; myocardial infarction or cerebrovascular accident possibly secondary to excessive hypotension in high risk patients (see WARNINGS, Hypotension); pulmonary embolism and infarction, arrhythmias (including ventricular tachycardia, atrial tachycardia, atrial fibrillation, bradycardia and premature ventricular contractions), palpitations, transient ischemic attacks, paroxysmal nocturnal dyspnea, orthostatic hypotension, decreased blood pressure, peripheral edema, vasculitis.

Digestive: Pancreatitis, hepatitis (hepatocellular or cholestatic jaundice) , vomiting, gastritis, dyspepsia, heartburn, gastrointestinal cramps, constipation, flatulence, dry mouth.

Hematologic: Rare cases of bone marrow depression, hemolytic anemia, leukopenia/neutropenia and thrombocytopenia.

Endocrine: Diabetes mellitus.

Metabolic: Weight loss, dehydration, fluid overload, gout, weight gain.

Cases of hypoglycemia in diabetic patients on oral antidiabetic agents or insulin have been reported in post-marketing experience.

Musculoskeletal: Arthritis, arthralgia, neck pain, hip pain, low back pain, joint pain, leg pain, knee pain, shoulder pain, arm pain, lumbago.

Nervous System/Psychiatric: Stroke, ataxia, memory impairment, tremor, peripheral neuropathy (e.g., dysesthesia), spasm, paresthesia, confusion, insomnia, somnolence, hypersomnia, irritability, nervousness and mood alterations (including depressive symptoms).

Respiratory System: Malignant lung neoplasms, hemoptysis, pulmonary infiltrates, bronchospasm, asthma, pleural effusion, pneumonia, eosinophilic pneumonitis, bronchitis, wheezing, orthopnea, painful respiration, epistaxis, laryngitis, sinusitis, pharyngeal pain, pharyngitis, rhinitis, rhinorrhea.

Skin: Urticaria, alopecia, herpes zoster, photosensitivity, skin lesions, skin infections, pemphigus, erythema, flushing, diaphoresis, cutaneous pseudolymphoma. Other severe skin reactions have been reported rarely, including toxic epidermal necrolysis and Stevens-Johnson syndrome; causal relationship has not been established.

Special Senses: Visual loss, diplopia, blurred vision, tinnitus, photophobia, taste disturbances.

Urogenital System: Acute renal failure, oliguria, anuria, uremia, progressive azotemia, renal dysfunction , pyelonephritis, dysuria, urinary tract infection, breast pain.

Miscellaneous: A symptom complex has been reported which may include a positive ANA, an elevated erythrocyte sedimentation rate, arthralgia/arthritis, myalgia, fever, vasculitis, eosinophilia and leukocytosis. Rash, photosensitivity or other dermatological manifestations may occur alone or in combination with these symptoms.

Angioedema: Angioedema has been reported in patients receiving Lisinopril with an incidence higher in Black than in non-Black patients. Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis and/or larynx occurs, treatment with Lisinopril should be discontinued and appropriate therapy instituted immediately.

In rare cases, intestinal angioedema has been reported in post marketing experience.

Hypotension: In hypertensive patients, hypotension occurred in 1.2% and syncope occurred in 0.1% of patients with an incidence higher in Black than in non-Black patients. Hypotension or syncope was a cause of discontinuation of therapy in 0.5% of hypertensive patients. In patients with heart failure, hypotension occurred in 5.3% and syncope occurred in 1.8% of patients. These adverse experiences were possibly dose-related (see above data from ATLAS Trial) and caused discontinuation of therapy in 1.8% of these patients in the symptomatic trials. In patients treated with Lisinopril for six weeks after acute myocardial infarction, hypotension (systolic blood pressure ≤100 mmHg) resulted in discontinuation of therapy in 9.7% of the patients.

***Fetal/Neonatal Morbidity and Mortality***

*Cough*

Pediatric Patients: No relevant differences between the adverse experience profile for pediatric patients and that previously reported for adult patients were identified.

*Clinical Laboratory Findings*

Serum Electrolytes: Hyperkalemia , hyponatremia.

Creatinine, Blood Urea Nitrogen: Minor increases in blood urea nitrogen and serum creatinine, reversible upon discontinuation of therapy, were observed in about 2.0% of patients with essential 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 approximately 11.6% of patients with heart failure on concomitant diuretic therapy.

Frequently, these abnormalities resolved when the dosage of the diuretic was decreased.

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. Hemolytic anemia has been reported; a causal relationship to lisinopril cannot be excluded.

Liver Function Tests: Rarely, elevations of liver enzymes and/or serum bilirubin have occurred.

In hypertensive patients, 2.0% discontinued therapy due to laboratory adverse experiences, principally elevations in blood urea nitrogen (0.6%), serum creatinine (0.5%) and serum potassium (0.4%).

In the heart failure trials, 3.4% of patients discontinued therapy due to laboratory adverse experiences; 1.8% due to elevations in blood urea nitrogen and/or creatinine and 0.6% due to elevations in serum potassium.

In the myocardial infarction trial, 2.0% of patients receiving Lisinopril discontinued therapy due to renal dysfunction (increasing creatinine concentration to over 3 mg/dL or a doubling or more of the baseline serum creatinine concentration); less than 1.0% of patients discontinued therapy due to other laboratory adverse experiences: 0.1% with hyperkalemia and less than 0.1% with hepatic enzyme alterations.

***Adverse drug reactions from spontaneous reports and literature cases - post-marketing experience***

***Amlodipine***

Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

The following postmarketing event has been reported infrequently where a causal relationship is uncertain: gynaecomastia. In postmarketing experience, jaundice and hepatic enzyme elevations (mostly consistent with cholestasis or hepatitis), in some cases severe enough to require hospitalization, have been reported in association with use of amlodipine. Postmarketing reporting has also revealed a possible association between extrapyramidal disorder and amlodipine.

Amlodipine has been used safely in patients with chronic obstructive pulmonary disease, well-compensated congestive heart failure, coronary artery disease, peripheral vascular disease, diabetes mellitus, and abnormal lipid profiles.

***Lisinopril***

The following adverse reactions have been identified during post-approval use of lisinopril that are not included in other sections of labeling. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Other reactions include:

Metabolism and nutrition disorders: Hyponatremia, cases of hypoglycemia in diabetic patients on oral antidiabetic agents or insulin

Nervous system and psychiatric disorders: Mood alterations (including depressive symptoms), mental confusion, hallucinations

Skin and subcutaneous tissue disorders: Psoriasis.

If you experience any side effects, talk to your doctor or pharmacist or write to drugsafety@cipla.com. You can also report side effects directly via the national pharmacovigilance program of India by calling on 1800 180 3024 or you can report to Cipla Ltd. on 1800 267 7779. By reporting side effects, you can help provide more information on the safety of this product.

## Overdose

### Amlodipine

Overdosage might be expected to cause excessive peripheral vasodilation with marked hypotension and possibly a reflex tachycardia. In humans, experience with intentional overdosage of nebivolol is limited. Single oral doses of amlodipine maleate equivalent to 40 mg amlodipine/kg and 100 mg amlodipine/kg in mice and rats, respectively, caused deaths. Single oral amlodipine maleate doses equivalent to 4 or more mg amlodipine/kg or higher in dogs (11 or more times the maximum recommended human dose on a mg/m basis) caused a marked peripheral vasodilation and hypotension.

If massive overdose should occur, initiate active cardiac and respiratory monitoring. Frequent blood pressure measurements are essential. Should hypotension occur, provide cardiovascular support including elevation of the extremities and the judicious administration of fluids. If hypotension remains unresponsive to these conservative measures, consider administration of vasopressors (such as phenylephrine) with attention to circulating volume and urine output. As amlodipine is highly protein bound, hemodialysis is not likely to be of benefit.

### Lisinopril

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.

# Pharmacological Properties

## Mechanism of action

Amlodipine is a dihydropyridine calcium antagonist (calcium ion antagonist or slow-channel blocker) that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac

muscle. Experimental data suggest that amlodipine binds to both dihydropyridine and nondihydropyridine binding sites. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels. Amlodipine inhibits calcium ion influx across cell membranes selectively, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells. Negative inotropic effects can be detected in vitro but such effects have not been seen in intact animals at therapeutic doses. Serum calcium concentration is not affected by amlodipine. Within the physiologic pH range, amlodipine is an ionized compound (pKa=8.6), and its kinetic interaction with the calcium channel receptor is characterized by a gradual rate of association and dissociation with the receptor binding site, resulting in a gradual onset of effect. Amlodipine is a peripheral arterial vasodilator that acts directly on vascular smooth muscle to cause a reduction in peripheral vascular resistance and reduction in blood pressure.

The precise mechanisms by which amlodipine relieves angina have not been fully delineated, but are thought to include the following:

Exertional Angina: In patients with exertional angina, Amlodipine reduces the total peripheral resistance (afterload) against which the heart works and reduces the rate pressure product, and thus myocardial oxygen demand, at any given level of exercise.

Vasospasti Angina: Amlodipine has been demonstrated to block constriction and restore blood flow in coronary arteries and arterioles in response to calcium, potassium epinephrine, serotonin, and thromboxane A2 analog in experimental animal models and in human coronary vessels in vitro. This inhibition of coronary spasm is responsible for the effectiveness of Amlodipine in vasospastic (Prinzmetal’s or variant) angina.

Lisinopril inhibits angiotensin-converting enzyme (ACE) in human subjects and animals. ACE is a peptidyl dipeptidase that catalyzes the conversion of angiotensin I to the vasoconstrictor substance, angiotensin II. Angiotensin II also stimulates aldosterone secretion by the adrenal cortex. The beneficial effects of lisinopril in hypertension and heart failure appear to result primarily from suppression of the renin-angiotensin-aldosterone system. Inhibition of ACE results in decreased plasma angiotensin II which leads to decreased vasopressor activity and to decreased aldosterone secretion. The latter decrease may result in a small increase of serum potassium. In hypertensive patients with normal renal function treated with Lisinopril alone fo up to 24 weeks, the mean increase in serum potassium was approximately 0.1 mEq/L; however, approximately 15% of patients had increases greater than 0.5 mEq/L and approximately 6% had a decrease greater than 0.5 mEq/L. In the same study, patients treated with Lisinopril and hydrochlorothiazide for up to 24 weeks had a mean decrease in serum potassium of 0.1 mEq/L; approximately 4% of patients had increases greater than 0.5 mEq/L and approximately 12% had a decrease greater than 0.5 mEq/L. Removal of angiotensin II negative feedback on renin secretion leads to increased plasma renin activity. ACE is identical to kininase, an enzyme that degrades bradykinin. Whether increased levels of bradykinin, a potent vasodepressor peptide, play a role in the therapeutic effects of Lisinopril remains to be elucidated.

While 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. Although Lisinopril was antihypertensive in all races studied, Black hypertensive patients (usually a low-renin hypertensive population) had a smaller average response to monotherapy than non-Black patients. Concomitant administration of L and hydrochlorothiazide further reduced blood pressure in Black and non-Black patients and any racial differences in blood pressure response were no longer evident.

## Pharmacodynamic Properties

### *Amlodipine*

#### ***Haemodynamics***

Following administration of therapeutic doses to patients with hypertension, amlodipine produces vasodilation resulting in a reduction of supine and standing blood pressures. These decreases in blood pressure are not accompanied by a significant change in heart rate or plasma catecholamine levels with chronic dosing.

Although the acute intravenous (IV) administration of amlodipine decreases arterial blood pressure and increases heart rate in haemodynamic studies of patients with chronic stable angina, chronic oral administration of amlodipine in clinical trials did not lead to clinically significant changes in heart rate or blood pressures in normotensive patients with angina.

With chronic once-daily oral administration, antihypertensive effectiveness is maintained for at least 24 hours. Plasma concentrations correlate with effect in both young and elderly patients. The magnitude of reduction in blood pressure with amlodipine is also correlated with the height of pre-treatment elevation; thus, individuals with moderate hypertension (diastolic pressure 105–114 mmHg) had about a 50% greater response than patients with mild hypertension (diastolic pressure 90–104 mmHg). Normotensive subjects experienced no clinically significant change in blood pressures (+1/-2 mmHg).

In hypertensive patients with normal renal function, therapeutic doses of amlodipine resulted in a decrease in renal vascular resistance and an increase in glomerular filtration rate and effective renal plasma flow without change in filtration fraction or proteinuria.

As with other calcium channel blockers, haemodynamic measurements of cardiac function at rest and during exercise (or pacing) in patients with normal ventricular function treated with amlodipine have generally demonstrated a small increase in cardiac index without significant influence on dP/dt or on left ventricular end diastolic pressure or volume. In haemodynamic studies, amlodipine has not been associated with a negative inotropic effect when administered in the therapeutic dose range to intact animals and humans, even when co-administered with beta-blockers to humans. Similar findings, however, have been observed in normals or well-compensated patients with heart failure with agents possessing significant negative inotropic effects.

#### ***Electrophysiologic Effects***

Amlodipine does not change sinoatrial nodal function or atrioventricular conduction in intact animals or humans. In patients with chronic stable angina, IV administration of 10 mg did not significantly alter A-H and H-V conduction and sinus node recovery time after pacing. Similar results were obtained in patients receiving amlodipine and concomitant beta-blockers. In clinical studies in which amlodipine was administered in combination with beta-blockers to patients with either hypertension or angina, no adverse effects on electrocardiographic parameters were observed. In clinical trials with angina patients alone, amlodipine therapy did not alter electrocardiographic intervals or produce higher degrees of atrioventricular) blocks.

### *Lisinopril*

Lisinopril inhibits ACE in human subjects and animals. ACE is a peptidyl dipeptidase that catalyzes the conversion of angiotensin I to the vasoconstrictor substance, angiotensin II. Angiotensin II also

stimulates aldosterone secretion by the adrenal cortex. The beneficial effects of lisinopril in hypertension and heart failure appear to result primarily from suppression of the renin-angiotensi--aldosterone system (RAAS). Inhibition of ACE results in decreased plasma angiotensin II which leads to decreased vasopressor activity and to decreased aldosterone secretion. The latter decrease may result in a small increase of serum potassium. In hypertensive patients with normal renal function treated with Lisinopril alone for up to 24 weeks, the mean increase in serum potassium was approximately 0.1 mEq/L; however, approximately 15% of patients had increases greater than 0.5 mEq/L and approximately 6% had a decrease greater than 0.5 mEq/L. In the same study, patients treated with lisinopril and hydrochlorothiazide for up to 24 weeks had a mean decrease in serum potassium of 0.1 mEq/L; approximately 4% of patients had increases greater than 0.5 mEq/L and approximately 12% had a decrease greater than 0.5 mEq/L. Removal of angiotensin II negative feedback on renin secretion leads to increased plasma renin activity.

ACE is identical to kininase, an enzyme that degrades bradykinin. Whether increased levels of bradykinin, a potent vasodepressor peptide, play a role in the therapeutic effects of lisinopril remains to be elucidated.

While the mechanism through which lisinopril lowers blood pressure is believed to be primarily suppression of the RAAS, lisinopril is antihypertensive even in patients with low-renin hypertension. Although lisinopril was antihypertensive in all races studied, Black hypertensive patients (usually a low-renin hypertensive population) had a smaller average response to monotherapy than non-Black patients.

Concomitant administration of lisinopril and hydrochlorothiazide further reduced blood pressure in Black and non-Black patients and any racial differences in blood pressure response were no longer evident. 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.

## Pharmacokinetic Properties

***Amlodipine***

After oral administration of therapeutic doses of amlodipine, absorption produces peak plasma concentrations between 6 and 12 hours. Absolute bioavailability has been estimated to be between 64 and 90%. The bioavailability of amlodipine is not altered by the presence of food. Amlodipine is extensively (about 90%) converted to inactive metabolites via hepatic metabolism with 10% of the parent compound and 60% of the metabolites excreted in the urine. Ex vivo studies have shown that approximately 93% of the circulating drug is bound to plasma proteins in hypertensive patients.

Elimination from the plasma is biphasic with a terminal elimination half-life of about 30–50 hours. Steady-state plasma levels of amlodipine are reached after 7–8 days of consecutive daily dosing.

The pharmacokinetics of amlodipine is not significantly influenced by renal impairment. Patients with renal failure may, therefore, receive the usual initial dose.

Elderly patients and patients with hepatic insufficiency have decreased clearance of amlodipine with a resulting increase in area under curve (AUC) of approximately 40–60%, and a lower initial dose may be required. A similar increase in AUC was observed in patients with moderate-to-severe heart failure.

*Pediatric Patients*

Sixty-two hypertensive patients aged 6 to 17 years received doses of amlodipine between 1.25 mg and 20 mg. Weight-adjusted clearance and volume of distribution were similar to values in adults.

***Lisinopril***
Adult Patients: 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 (5-80 mg). The absolute bioavailability of lisinopril is reduced to 16% in patients with stable NYHA Class II-IV congestive heart failure, and the volume ofdistribution 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. In a multicenter, open-label pharmacokinetic study of daily oral lisinopril in 22 pediatric hypertensive patients with stable kidney transplant (ages 7-17 years; estimated glomerular filtration rate > 30 mL/min/1.73 m2), dose normalized exposures were in the range reported previously in children without a kidney transplant

# Nonclinical Properties

## Animal Toxicology and Pharmacology

### *Amlodipine*

Carcinogenesis, Mutagenesis, Impairment of Fertility: Rats and mice treated with amlodipine maleate in the diet for up to two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 amlodipine mg/kg/day, showed no evidence of a carcinogenic effect of the drug.

For the mouse, the highest dose was, on a mg/m2 basis, similar to the maximum recommended human dose of 10 mg amlodipine/day. For the rat, the highest dose was, on a mg/m2 basis, about twice the maximum recommended human dose. Mutagenicity studies conducted with amlodipine maleate revealed no drug related effects at either the gene or chromosome level. There was no effect on the fertility of rats treated orally with amlodipine maleate (males for 64 days and females for 14 days prior to mating) at doses up to 10 mg amlodipine/kg/day (8 times the maximum recommended human dose 3 of 10 mg/day on a mg/m2 basis).

***Lisinopril***

There was no evidence of a tumorigenic effect when lisinopril was administered for 105 weeks to male and female rats at doses up to 90 mg/kg/day (about 56 or 9 times2 the maximum recommended daily human dose, based on body weight and body surface area, respectively). There was no evidence of carcinogenicity when lisinopril was administered for 92 weeks to (male and female) mice at doses up to 135 mg/kg/dayLisinopril did not produce single strand DNA breaks in an in vitro alkaline elution rat hepatocyte assay. In addition, lisinopril did not produce increases in chromosomal aberrations in an in vitro test in Chinese hamster ovary cells or in an in vivo study in mouse bone marrow. There were no adverse effects on reproductive performance in male and female rats treated with up to 300 mg/kg/day of lisinopril.

# Description

**AMLOPRES-L** is a combination of amlodipine, a dihydropyridine calcium antagonist and lisinopril, an angiotensin converting enzyme (ACE) inhibitor. The combination provides additive reduction in blood pressure in hypertension patients.

# Pharmaceutical Particulars

Blister pack of 10 Tablets

Amlopres -L

Amlodipine .....5 mg

Lisinopril.....5 mg

## Incompatibilities

None Known

## Shelf-Life

**Amlopres-L-2 years**

## Packaging Information

**AMLOPRES-L:** Blister pack of 10 tablets

## Storage and Handling Instructions

Store in a cool, dry place away from light.

# Patient Counseling Information

**AMLOPRES -L** 5 mg/5 mg tablets

**Read all this leaflet carefully before you start taking this medicine because it contains important information for you.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse.

**What is in this leaflet**



1. ***What AMLOPRES L is and what it is used for***

**AMLOPRES L** is a type of medicine known as a calcium channel blocker (CCB) and angiotensin converting enzyme inhibitor (ACEi) . It is used to treat high blood pressure (hypertension) and a type of chest pain called angina. It can be used by itself or with other medicines to treat these conditions. High Blood Pressure (hypertension) High blood pressure comes from blood pushing too hard against your blood vessels. **AMLOPRES L** relaxes your blood vessels, which lets your blood flow more easily and helps lower your blood pressure. Drugs that lower blood pressure lower your risk of having a stroke or heart attack.  Angina is a pain or discomfort that keeps coming back when part of your heart does not get enough blood. Angina feels like a pressing or squeezing pain, usually in your chest under the breastbone. Sometimes you can feel it in your shoulders, arms, neck, jaws, or back. **AMLOPRES L** can relieve this pain.

***Who should not use AMLOPRES L***

Do not use **AMLOPRES L** if you are allergic to amlodipine and lisinopril (the active ingredient in  **AMLOPRES L**), or to the inactive ingredients. Your doctor or pharmacist can give you a list of these ingredient

1. ***What should I tell my doctor before taking AMLOPRES L?***

Tell your doctor about any prescription and non-prescription medicines you are taking, including natural or herbal remedies.

Tell your doctor if you:

• ever had heart disease

• ever had liver problems

• are pregnant, or plan to become pregnant.

Your doctor will decide if **AMLOPRES L** is the best treatment for you.

***How should I take AMLOPRES L?***

Take **AMLOPRES L** once a day, with or without food.

• It may be easier to take your dose if you do it at the same time every day, such as with breakfast or dinner, or at bedtime. Do not take more than one dose of **AMLOPRES L** at a time.

• If you miss a dose, take it as soon as you remember. Do not take **AMLOPRES L** if it has been more than 12 hours since you missed your last dose. Wait and take the next dose at your regular time.

• Other medicines: You can use nitroglycerin and **AMLOPRES L** together. If you take nitroglycerin for angina, don't stop taking it while you are taking **AMLOPRES L**.

• While you are taking **AMLOPRES L**, do not stop taking your other prescription medicines, including any other blood pressure medicines, without talking to your doctor.

• If you took too much **AMLOPRES L**, call your doctor or Poison Control Center, or go to the nearest hospital emergency room right away.

***What should I avoid while taking AMLOPRES L***?

• Do not start any new prescription or non-prescription medicines or supplements, unless you check with your doctor first

Reporting of side effects.

If you experience any side effects, talk to your doctor or pharmacist or write to drugsafety@cipla.com. You can also report side effects directly via the national pharmacovigilance program of India by calling on 1800 180 3024 or you can report to Cipla Ltd. on 1800 267 7779. By reporting side effects, you can help provide more information on the safety of this product.

1. ***How to store* AMLOPRES L**

Keep **AMLOPRES L** away from children. Store **AMLOPRES L** Tablets at room temperature (between 59° and 86°F). Keep **AMLOPRES L** out of the light. Do not store in the bathroom. Keep **AMLOPRES L** in a dry place.

1. ***Contents of the pack and other information***

The active substances are amlodipine and atenolol.

- Each uncoated tablet contains: Amlodipine besylate equivalent to Amlodipine 5 mg and Lisinopril 5 mg.

# Details of Manufacturer

**M/S Cipla Ltd. Mumbai central, Mumbai-400008**

## Details of Permission or License Number with Date

**M.L.M/447/2007**

## Date of Revision

10/12/2019