Amlodipine plus Lisinopril Tablets

AMLOPRES-L

COMPOSITION
AMLOPRES-L
Each uncoated tablet contains:
Amlodipine besylate equivalent to Amlodipine 5 mg and Lisinopril USP equivalent to Lisinopril (anhydrous) 5 mg

DOSAGE FORM
Tablet

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.

PHARMACOLOGY
Pharmacodynamics
Amlodipine
Amlodipine inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. Experimental data suggest that amlodipine binds to both dihydropyridine and non-dihydropyridine 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.

Hemodynamics: 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.

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 the glomerular filtration rate and effective renal plasma flow without change in filtration fraction or proteinuria.

As with other calcium channel blockers, hemodynamic 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 hemodynamic studies, amlodipine has not been associated with a negative inotropic effect when administered in the therapeutic dose range to intact animals and man, even when co-administered with beta-blockers to man. Similar findings, however, have been observed in normal 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 man. In clinical studies in which amlodipine was administered in combination with beta-blockers to patients with hypertension, no adverse effects on electrocardiographic parameters were observed.

Lisinopril

The beneficial effects of lisinopril in hypertension appear to result primarily from suppression of the renin-angiotensin-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. 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.

Administration of lisinopril to patients with hypertension results in a reduction of 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 six 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 six hours after dosing. In some patients, achievement of optimal blood pressure reduction may require two to four weeks of therapy.

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 pre-treatment levels.
Lisinopril had similar effectiveness and adverse effects in younger and older (>65 years) patients. It was less effective in Blacks than in Caucasians.

In hemodynamic studies in patients with essential hypertension, blood pressure reduction was accompanied by a reduction in peripheral arterial resistance with little or no change in cardiac output and in heart rate.

In patients with renovascular hypertension, lisinopril has been shown to be well tolerated and effective in controlling blood pressure.

Pharmacokinetics
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 to 8 days of consecutive daily dosing.

The pharmacokinetics of amlodipine are 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 the area under the plasma concentration time 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: Following oral administration of lisinopril, peak serum concentrations of lisinopril occur within about 7 hours, although there was a trend to a small delay in time taken to reach peak serum concentrations in acute myocardial infarction patients. 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. 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). Lisinopril absorption is not influenced by the presence of food in the gastrointestinal tract.

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 changed little. With greater impairment, however, peak and trough lisinopril levels increase, time to peak concentration increases and time to attain steady state is prolonged. Older patients, on average, have (approximately doubled) higher blood levels and AUC than younger patients. 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 m^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. 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.

INDICATIONS

AMLOPRES-L is indicated in the treatment of mild to moderate hypertension. It is also indicated in hypertension not responding to monotherapy with ACE inhibitors or calcium antagonists. It may also be substituted for the titrated doses of the individual components.

DOSAGE AND 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 and in patients with hereditary or idiopathic angioedema

WARNINGS AND PRECAUTIONS

Drug Interactions

Diuretics*:* Patients on diuretics may occasionally experience an excessive reduction of blood pressure after initiation of therapy with this combination. The possibility of hypotensive effects can be minimized by either discontinuing the combination or increasing the salt intake prior to initiation of treatment.

Agents Increasing Serum Potassium: Lisinopril attenuates potassium loss caused by thiazide-type diuretics. If concomitant use of these agents is indicated, they should be used with caution, and with frequent monitoring of serum potassium.

Lithium*:* Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving ACE inhibitors during therapy with lithium.

AMLOPRES-L and lithium should be co-administered with caution, and frequent monitoring of serum lithium levels is recommended.

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs): In some patients with compromised renal function who are being treated with NSAIDs, the co-administration of lisinopril may result in a further deterioration of renal function. These effects are usually reversible. NSAIDs blunt the antihypertensive effect of ACE inhibitors, including lisinopril, and this should be given consideration in patients taking NSAIDs concomitantly with **AMLOPRES-L**. Indomethacin may reduce the antihypertensive efficacy of lisinopril.

Aggravation of Angina

Rarely, patients, particularly those with severe obstructive coronary artery disease, have developed increased frequency, duration and/or severity of angina or acute myocardial infarction on starting calcium channel blocker therapy, or at the time of dosage increase.

Congestive Heart Failure
In general, calcium channel blockers should be used with caution in patients with heart failure. Placebo-controlled trials of amlodipine in patients with New York Heart Association (NYHA) Class III or IV heart failure showed no overall adverse effect on survival or cardiac morbidity. In NYHA Class II/III heart failure patients, there was no evidence of worsened heart failure based on measures of exercise tolerance, NYHA classification, symptoms, or left ventricular ejection fraction.

Renal Impairment
AMLOPRES-L should be used with caution in patients with severe renal disease. As a consequence of inhibition of the RAAS, changes in renal function may be anticipated in susceptible individuals. In hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine may occur, which is usually reversible. When such patients are treated with **AMLOPRES-L**, renal function should be monitored during the first few weeks of therapy. Evaluation of patients with hypertension should always include assessment of renal function.

Hepatic Impairment
Caution should be exercised when administering **AMLOPRES-L** in patients with severe liver damage because of prolongation of the elimination half-life of amlodipine.

Pregnancy
When pregnancy is detected, ACE inhibitors should be discontinued as soon as possible. In a published retrospective epidemiological study, infants whose mother had taken an ACE inhibitor drug during the first trimester of pregnancy appeared to have an increased risk of major congenital malformations compared with infants whose mothers had not undergone first trimester exposure to ACE inhibitor drugs. The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function. If oligohydramnios is observed, lisinopril should be discontinued unless it is considered lifesaving for the mother. Rarely (probably less often than once in every thousand pregnancies), no alternative to ACE inhibitors will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intraamniotic environment. Hence, the combination is contraindicated in pregnancy.

Lactation
It is not known whether lisinopril or amlodipine is excreted in human milk. In the absence of this information, it is recommended that nursing be discontinued while the combination is administered.

Pediatric Use
Safety and effectiveness of **AMLOPRES-L** in children < 6 years of age have not been established.

Geriatric Use
Clinical studies of amlodipine and lisinopril monotherapy in patients with hypertension did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other clinical experience in this population 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 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.
Pharmacokinetic studies indicate that maximum blood levels and area under plasma concentration curve (AUC) are doubled in elderly patients treated with lisinopril. Lisinopril is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection. Evaluation of patients with hypertension should always include assessment of renal function.

UNDESIRABLE EFFECTS
The combination of amlodipine and lisinopril is well tolerated. Angioneurotic edema has been reported with ACE inhibitors. In such cases, the combination should be discontinued immediately. Other side effects include nausea, headache, dizziness, cough, diarrhea, fatigue, rash, edema, flushing, palpitations, and asthenia.

OVERDOSAGE
The most likely manifestation of overdosage of lisinopril would be hypotension, for which the usual treatment would be intravenous infusion of normal saline solution. Lisinopril can be removed by hemodialysis.

If massive overdose of amlodipine should occur, active cardiac and respiratory monitoring should be instituted. Frequent blood pressure measurements are essential. Should hypotension occur, cardiovascular support including elevation of the extremities and the judicious administration of fluids should be initiated. If

hypotension remains unresponsive to these conservative measures, administration of vasopressors (such as phenylephrine) should be considered with attention to circulating volume and urine output. Intravenous calcium gluconate may help to reverse the effects of calcium entry blockade. As amlodipne is highly protein bound, hemodialysis is not likely to be of benefit.

PACKAGING INFORMATION

AMLOPRES-L Blister pack of 10 tablets

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