AMLOPRES-Z

COMPOSITION AMLOPRES-Z
Each tablet contains:
Amlodipine Besylate equivalent to Amlodipine 5 mg and Losartan Potassium 50 mg.

DOSAGE FORM
Tablet

DESCRIPTION AMLOPRES-Z is a combination of amlodipine, a dihydropyridine calcium antagonist and losartan, an angiotensin II receptor (type AT₁) antagonist. 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.

**Losartan**
Losartan and its principal active metabolite block the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT₁ receptor found in many tissues, (e.g., vascular smooth muscle, adrenal gland). Both losartan and its principal active metabolite do not exhibit any partial agonist activity at the AT₁ receptor and have much greater affinity (about 1000-fold) for the AT₁ receptor than for the AT₂ receptor. In *vitro* binding studies indicate that losartan is a reversible, competitive inhibitor of the AT₁ receptor. The active metabolite is 10 to 40 times more potent by weight than losartan and appears to be a reversible, non-competitive inhibitor of the AT₁ receptor.

Neither losartan nor its active metabolite inhibits the angiotensin converting enzyme [ACE (kininase II, the enzyme that converts angiotensin I to angiotensin II and degrades bradykinin)]; nor do they bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.
Losartan inhibits the pressor effect of angiotensin II (as well as angiotensin I) infusions. A dose of 100 mg inhibits the pressor effect by about 85% at peak with 25-40% inhibition persisting for 24 hours. Removal of the negative feedback of angiotensin II causes a 2- to 3-fold rise in plasma renin activity and consequent rise in angiotensin II plasma concentration in hypertensive patients. Losartan does not affect the response to bradykinin, whereas ACE inhibitors increase the response to bradykinin. Aldosterone plasma concentrations fall following losartan administration. In spite of the effect of losartan on aldosterone secretion, very little effect on serum potassium was observed.

In a single-dose study in normal volunteers, losartan had no effects on the glomerular filtration rate, renal plasma flow or filtration fraction. In multiple-dose studies in hypertensive patients, there were no notable effects on systemic or renal prostaglandin concentrations, fasting triglycerides, total cholesterol or high density lipoprotein (HDL) cholesterol or fasting glucose concentrations. There was a small uricosuric effect leading to a minimal decrease in serum uric acid (mean decrease <0.4 mg/dL) during chronic oral administration.

Analysis of age, gender, and race subgroups of patients showed that men and women, and patients over and under 65, had generally similar responses. Losartan was effective in reducing blood pressure regardless of race, although the effect was somewhat less in Black patients (usually a low-renin population).

The effect of losartan is substantially present within one week but in some studies the maximal effect occurred in 3-6 weeks. In long-term follow-up studies (without placebo control) the effect of losartan appeared to be maintained for up to a year. There is no apparent rebound effect after abrupt withdrawal of losartan. There was essentially no change in average heart rate in losartan-treated patients in controlled trials.

No significant differences in the overall antihypertensive effect of losartan were detected when the patients were analyzed according to age (<, ≥12 years old) or gender.

**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.

**Losartan**

Losartan is an orally active agent that undergoes substantial first-pass metabolism by cytochrome P450 enzymes. It is converted, in part, to an active carboxylic acid metabolite that is responsible for most of the angiotensin II receptor antagonism that follows losartan treatment. Losartan metabolites have been identified in human plasma and urine. In addition to the active carboxylic acid metabolite, several inactive metabolites are formed. Following oral and intravenous administration of 14C-labeled losartan potassium, circulating plasma radioactivity is primarily attributed to losartan and its active metabolite. In *vitro* studies indicate that cytochrome P450 2C9 and 3A4 are involved in the biotransformation of losartan to its metabolites. Minimal conversion of losartan to the active metabolite (less than 1% of the dose compared to 14% of the dose in normal subjects) was seen in about one percent of individuals studied. The terminal half-life of losartan is about 2 hours and of the metabolite is about 6-9 hours.

The pharmacokinetics of losartan and its active metabolite are linear with oral losartan doses up to 200 mg and do not change over time. Neither losartan nor its metabolite accumulates in plasma upon repeated once-daily dosing.

Following oral administration, losartan is well absorbed (based on absorption of radiolabeled losartan) and undergoes substantial first-pass metabolism; the systemic bioavailability of losartan is approximately 33%. About 14% of an orally administered dose of losartan is converted to the active metabolite. Mean peak concentrations of losartan and its active metabolite are reached in 1 hour and in 3-4 hours, respectively. While maximum plasma concentrations of losartan and its active metabolite are approximately equal, the AUC of the metabolite is about 4 times as great as that of losartan. A meal slows absorption of losartan and decreases its $C_{\text{max}}$, but has only minor effects on losartan AUC or on the AUC of the metabolite (about 10% decreased).
The pharmacokinetics of losartan and its active metabolite were also determined after intravenous doses of each component separately in healthy volunteers. The volume of distribution of losartan and the active metabolite is about 34 liters and 12 liters, respectively. Total plasma clearance of losartan and the active metabolite is about 600 mL/min and 50 mL/min, respectively, with renal clearance of about 75 mL/min and 25 mL/min, respectively. After single doses of losartan administered orally, about 4% of the dose is excreted unchanged in the urine and about 6% is excreted in urine as active metabolite. Biliary excretion contributes to the elimination of losartan and its metabolites. Following oral 14C-labeled losartan, about 35% of radioactivity is recovered in the urine and about 60% in the feces. Following an intravenous dose of 14C-labeled losartan, about 45% of radioactivity is recovered in the urine and 50% in the feces.

Both losartan and its active metabolite are highly bound to plasma proteins, primarily albumin, with plasma-free fractions of 1.3% and 0.2%, respectively. Plasma protein binding is constant over the concentration range achieved with recommended doses. Studies in rats indicate that losartan crosses the blood-brain barrier poorly, if at all.

**Special Populations**

**Pediatric:** Pharmacokinetics of losartan and its active metabolite were generally similar across the studied age groups and similar to historical pharmacokinetic data in adults.

**Geriatrics and Gender:** Losartan pharmacokinetics have been investigated in the elderly (65-75 years) and in both genders. Plasma concentrations of losartan and its active metabolite are similar in elderly and young hypertensives. Plasma concentrations of losartan were about twice as high in female hypertensives as male hypertensives, but concentrations of the active metabolite were similar in males and females. No dosage adjustment is necessary.

**Renal impairment:** Following oral administration, plasma concentrations and AUCs of losartan and its active metabolite are increased by 50-90% in patients with mild (creatinine clearance of 50-74 mL/min) or moderate (creatinine clearance 30-49 mL/min) renal insufficiency. In this study, renal clearance was reduced by 55-85% for both losartan and its active metabolite in patients with mild or moderate renal insufficiency. Neither losartan nor its active metabolite can be removed by hemodialysis. No dosage adjustment is necessary for patients with renal impairment unless they are volume-depleted.

**Hepatic impairment:** Following oral administration in patients with mild to moderate alcoholic cirrhosis of the liver, plasma concentrations of losartan and its active metabolite were, respectively, 5 times and about 1.7 times those in young male volunteers. Compared to normal subjects, the total plasma clearance of losartan in patients with hepatic insufficiency was about 50% lower and the oral bioavailability was about two times higher. A lower starting dose is recommended for patients with a history of hepatic impairment.
INDICATION
AMLOPRES-Z is indicated for the treatment of mild to moderate hypertension. It is also indicated in hypertension not responding to monotherapy with calcium antagonists or angiotensin II receptor 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
The combination is contraindicated in patients who are hypersensitive to any component of this product.

WARNINGS AND PRECAUTIONS
Drug Interactions
Rifampin: Rifampin, an inducer of drug metabolism, decreased the concentrations of losartan and its active metabolite.
Fluconazole: Fluconazole, an inhibitor of P450 2C9, decreased active metabolite concentration and increased losartan concentration.
Agents That Increase Serum Potassium: As with other drugs that block angiotensin II or its effects, concomitant use of potassium-sparing diuretics, potassium supplements or salt substitutes containing potassium may lead to increases in serum potassium.
Lithium: Losartan reduces lithium excretion; hence, serum lithium levels should be monitored carefully if lithium salts are to be co-administered with AMLOPRES-Z.
Non-Steroidal Anti-Inflammatory Agents (NASIDs) Including Selective Cyclooxygenase-2 Inhibitors: In some patients with compromised renal function who are being treated with NSAIDs, including those that selectively inhibit cyclooxygenase-2 inhibitors (COX-2 inhibitors), the co-administration of losartan may result in a further deterioration of renal function. These effects are usually reversible. Reports suggest that NSAIDs, including selective COX-2 inhibitors, may diminish the antihypertensive effect of losartan. This interaction should be given consideration in patients taking NSAIDs, including selective COX-2 inhibitors, concomitantly with AMLOPRES-Z.

Hypotension
Excessive fall of blood pressure can occur with amlodipine in some patients, especially the elderly. In patients who are intravascularly volume-depleted (e.g., those treated with diuretics), symptomatic hypotension may occur after initiation of therapy with losartan. These conditions should be corrected prior to administration of AMLOPRES-Z.

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.

**Electrolyte imbalance**
Electrolyte imbalances are common in patients with renal impairment, with or without diabetes, and should be addressed.

**Renal Impairment**
The combination should be used with caution in patients with severe renal disease. As a consequence of inhibiting the renin-angiotensin-aldosterone system (RAAS), changes in renal function have been reported in susceptible individuals treated with losartan; in some patients, these changes in renal function were reversible upon discontinuation of therapy.

In patients whose renal function may depend on the activity of the RAAS (e.g., patients with severe congestive heart failure), losartan treatment has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. Also, losartan treatment in patients with unilateral or bilateral renal artery stenosis was associated with increases in serum creatinine or blood urea nitrogen (BUN). In some patients, these effects were reversible upon discontinuation of therapy.

**Hepatic Impairment**
Caution should be exercised when administering the combination to patients with impaired hepatic function due to increase in the plasma concentration of the combination.

**Pregnancy**
Drugs that act directly on the RAAS can cause fetal and neonatal morbidity and death when administered to pregnant women. When pregnancy is detected, **AMLOPRES-Z** should be discontinued as soon as possible. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function.

**Lactation**
It is not known whether losartan or amlodipine is excreted in human milk. In the absence of this information, it is recommended that nursing may be discontinued while the combination is administered.
**Pediatric Use**
Safety and effectiveness in pediatric patients have not been established.

**UNDESIRABLE EFFECTS**
The combination of amlodipine and losartan is well tolerated. Side effects include nausea, headache, dizziness, abdominal pain, fatigue, flushing, palpitation and asthenia.

**OVERDOSAGE**
The most likely manifestation of overdosage could be hypotension and tachycardia; bradycardia could occur from parasympathetic stimulation. If massive overdose 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. The combination cannot be removed by dialysis.

**PACKAGING INFORMATION**
AMLOPRES-Z Blister pack of 10 tablets

*Last updated: 05/10*