Amlodipine & Losartan Potassium Tablets

Mylod-L®

5 mg/50 mg Film coated tablet
Antihypertensive Agent

PRODUCT DESCRIPTION:
Orange, Round, Biconvex, film-coated tablet.

FORMULATION/COMPOSITION:
Each film-coated tablet contains:
Amlodipine Besylate equivalent to Amlodipine.....5 mg
Losartan
Potassium.....50 mg

INDICATIONS:
Amlodipine and Losartan Potassium is indicated for the treatment of mild to moderate hypertension as substitution therapy in adult patients whose blood pressure is adequately controlled on the combination of amlodipine and Losartan Potassium, taken either as a single-component formulations or as a dual-component.

DOSAGE AND ADMINSTRATION:
Dosage:
The usual recommended dose is once daily. Also, the dosage cane be determined by a doctor based on the patient's response and condition. 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.

Method of administration:
Amlodipine and Losartan Potassium is taken orally.

CONTRAINDICATIONS:
Amlodipine and Losartan Potassium are contraindicated in patients with known hypersensitivity to Amlodipine and Losartan Potassium. It is also contraindicated in pregnant women (in their 2nd and 3rd trimester) and nursing mothers.

SPECIAL WARNING AND PRECAUTIONS:
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 Amlodipine-Losartan combination.
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.
Pediatric Use:
Safety and effectiveness in pediatric patients have not been established.

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTIONS
Rifampin: It is an inducer of drug metabolism, decreased the concentrations of losartan and its active metabolite.
Fluconazole: It's an inhibitor of **Cytochrome 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 Amlodipine-Losartan combination.
Non-Steroidal Anti-Inflammatory Agents (NSAIDs), 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 Amlodipine-Losartan combination.

USE IN SPECIFIC POPULATIONS:
Pregnancy and Lactation
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, Amlodipine and Losartan combination 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.
EFFECTS ON ABILITY TO DRIVE AND USE MACHINES:
Amlodipine can have minor or moderate influence on the ability to drive and use machines. If patients taking amlodipine suffer from dizziness, headache, fatigue or nausea and the ability to react may be impaired. Caution is recommended especially at the start of treatment.

UNDESIRABLE EFFECTS:
The combination of Amlodipine and Losartan is well tolerated. Side effects include nausea, headache, dizziness, abdominal pain, fatigue, flushing, palpitation and asthenia.

OVERDOSE:
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

PHARMACOLOGICAL PROPERTIES:
Pharmacodynamic properties:

Pharmacotherapeutic group: Angiotensin II receptor blockers (ARBs) and calcium channel blockers, ATC code: C09DB06

Amlodipine

Amlodipine is a dihydropyridine calcium channel blocker that inhibits calcium ion influx into vascular smooth muscle and cardiac muscle, with predominant selectivity for vascular tissue. It binds to both dihydropyridine and non-dihydropyridine sites, producing peripheral arterial vasodilation and reduction in peripheral vascular resistance, thereby lowering blood pressure. The drug provides a sustained antihypertensive effect over 24 hours with once-daily dosing and is not associated with significant reflex tachycardia or clinically relevant effects on cardiac conduction. Although mild negative inotropic effects are observed in vitro, they are not evident in vivo at therapeutic doses, and serum calcium levels remain unchanged.

Its gradual association and dissociation with calcium channels results in a slow onset of action. Amlodipine also increases renal blood flow and glomerular filtration rate without affecting proteinuria. In angina, it reduces myocardial oxygen demand in exertional angina by decreasing afterload, and relieves vasospastic angina by inhibiting coronary artery spasm and restoring coronary blood flow.

Losartan

Losartan is an orally active, selective angiotensin II receptor blocker (AT1 antagonist) that inhibits angiotensin II–mediated vasoconstriction, aldosterone secretion, and vascular smooth muscle proliferation, key mechanisms in hypertension. It acts in vascular smooth muscle, adrenal gland, kidneys, and heart, thereby reducing blood pressure. Neither losartan nor its active metabolite inhibits ACE, so bradykinin degradation is unaffected, avoiding bradykinin-related adverse effects. Both compounds show high selectivity for AT1 over AT2 receptors and lack partial agonist activity.

Its active metabolite (E-3174) is more potent and provides longer AT1 blockade; both show high selectivity for AT1 over AT2 receptors. AT1 blockade increases plasma renin and angiotensin II levels while reducing aldosterone, with minimal effect on serum potassium.

Antihypertensive effects begin within one week, reach maximum at 3–6 weeks, and are maintained with once-daily dosing over 24 hours, preserving circadian blood pressure rhythm. Blood pressure reduction is sustained without rebound on withdrawal, with no clinically significant effect on heart rate. Efficacy is consistent across age and gender, though response may be slightly reduced in Black patients.

Pharmacokinetic properties:

Amlodipine:

Absorption, distribution, plasma protein binding: After oral administration of therapeutic doses, Amlodipine is well absorbed with peak blood levels between 6–12 hours post dose. Absolute bioavailability has been estimated to be between 64 and 80%. The volume of distribution is approximately 21 L/kg. In vitro studies have shown that approximately 97.5% of amlodipine is bound to plasma proteins. The bioavailability of amlodipine is unaffected by food intake.

Biotransformation/elimination: The terminal plasma elimination half-life is about 35–50 hours and is consistent with once-daily dosing. Amlodipine is extensively metabolised by the liver to inactive metabolites, with 10% of the parent compound and 60% of metabolites excreted in urine.

Use in hepatic impairment: Very limited clinical data are available regarding amlodipine administration in patients with hepatic impairment. Patients with hepatic insufficiency have decreased clearance of amlodipine resulting in a longer half-life and an increase in AUC of approximately 40–60%.

Use in the elderly: The time to reach peak plasma concentrations of amlodipine is similar in elderly and younger subjects. Amlodipine clearance tends to be decreased with resulting increases in AUC and elimination half-life in elderly patients. Increases in AUC and elimination half-life in patients with congestive heart failure were as expected for the patient age group studied.

Use in children: A population PK study has been conducted in 74 hypertensive children aged from 1 to 17 years (with 34 patients aged 6–12 years and 28 patients aged 13–17 years) receiving amlodipine between 1.25 and 20 mg given either once or twice daily. In children 6–12 years and in adolescents 13–17 years, the typical oral clearance (CL/F) was 22.5 and 27.4 L/hr respectively in males and 16.4 and 21.3 L/hr respectively in females. Large variability in exposure between individuals was observed. Data reported in children below 5 years is limited.

Losartan:

Absorption

Following oral administration, Losartan is well absorbed and undergoes first-pass metabolism, forming an active carboxylic acid metabolite and other inactive metabolites. The systemic bioavailability of losartan tablets is approximately 33%. Mean peak concentrations of losartan and its active metabolite are reached in 1 hour and 3-4 hours, respectively.

Distribution

Both losartan and its active metabolite are ≥99% bound to plasma proteins, primarily albumin. The volume of distribution of losartan is 34 litres.

Biotransformation

About 14% of an intravenously- or orally-administered dose of losartan is converted to its active metabolite. Following oral and intravenous administration of 14C-labelled losartan potassium, circulating plasma radioactivity primarily is attributed to losartan and its active metabolite. Minimal conversion of losartan to its active metabolite was seen in about one percent of individuals studied. In addition to the active metabolite, inactive metabolites are formed.

Elimination

Plasma clearance of losartan and its active metabolite is about 600 ml/min and 50 ml/min, respectively. Renal clearance of losartan and its active metabolite is about 74 ml/min and 26 ml/min, respectively. When losartan is administered orally, about 4% of the dose is excreted unchanged in the urine, and about 6% of the dose is excreted in the urine as active metabolite. The pharmacokinetics of losartan and its active metabolite are linear with oral losartan potassium doses up to 200 mg. Following oral administration, plasma concentrations of losartan and its active metabolite decline poly-exponentially, with a terminal half-life of about 2 hours and 6-9 hours, respectively. During once-daily dosing with 100 mg, neither losartan nor its active metabolite accumulates significantly in plasma. Both biliary and urinary excretions contribute to the elimination of losartan and its metabolites. Following an oral dose/intravenous administration of 14C-labelled losartan in man, about 35%/43% of radioactivity is recovered in the urine and 58%/ 50% in the faeces.

Characteristics in patients:

In elderly hypertensive patients, plasma concentrations of losartan and its active metabolite are similar to those in younger patients. In female patients, losartan exposure may be up to twice that of males, while metabolite levels remain comparable between sexes.

In mild to moderate alcohol-induced hepatic cirrhosis, plasma concentrations of losartan and its active metabolite increase approximately 5-fold and 1.7-fold, respectively, compared to healthy subjects.

Renal impairment does not significantly affect plasma levels of the active metabolite, and losartan exposure remains largely unchanged in patients with creatinine clearance >10 mL/min. However, in haemodialysis patients, losartan AUC is approximately doubled, while metabolite levels are unchanged. Neither losartan nor its active metabolite is removed by haemodialysis.

Pharmacokinetics in pediatric patients:

The pharmacokinetics of losartan have been investigated in 50 hypertensive pediatric patients > 1 month to < 16 years of age following once daily oral administration of approximately 0.54 to 0.77 mg/ kg of losartan (mean doses). The results showed that the active metabolite is formed from losartan in all age groups. The results showed roughly similar pharmacokinetic parameters of losartan following oral administration in infants and toddlers, preschool children, school age children and adolescents. The pharmacokinetic parameters for the metabolite differed to a greater extent between the age groups. When comparing preschool children with adolescents these differences became statistically significant. Exposure in infants/ toddlers was comparatively high.

STORAGE CONDITION:

Store at or below 30°C

AVAILABILITY:

Alu-Alu blister pack x 15's (Box of 150's)

MANUFACTURED BY:

Quest Pharmaceuticals Pvt. Ltd.
Chhatapipara, Bara, Nepal.

MARKETING AUTHORIZATION HOLDER:

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Daan Sadan, Teku, Kathmandu, Nepal.