Rx AMLO-H 5/10
Amlodipine Tablets
5 mg/10 mg
2081855

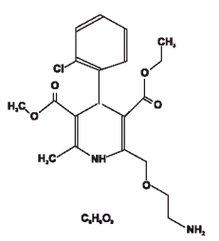
Rx **AMLO-H 5/10**
Amlodipine Tablets 5 mg/10 mg

AMLO-H 5 (Amlodipine Tablets 5 mg)
Each uncoated tablet contains Amlodipine 5 mg (equivalent to 6.934 mg of Amlodipine Besilate)

AMLO-H 10 (Amlodipine Tablets 10 mg)
Each uncoated tablet contains Amlodipine 10 mg (equivalent to 13.868 mg of Amlodipine Besilate)

DRUG DESCRIPTION

Amlodipine is the besylate salt of amlodipine, a long-acting calcium channel blocker. Amlodipine besylate is chemically described as 3-Ethy l-5-methyl (±)-2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate, monobenzenesulphonate. Its empirical formula is $C_{20}H_{25}ClN_2O_5 \cdot C_6H_6O_3S$, and its structural formula is:



Amlodipine besylate is a white crystalline powder. It is slightly soluble in water and sparingly soluble in ethanol. Amlodipine besylate Tablets are formulated as white tablets equivalent to 5 and 10 mg of amlodipine for oral administration. In addition to the active ingredient, amlodipine besylate, each tablet contains the following inactive ingredients: microcrystalline cellulose, Silica, Colloidal Anhydrous and Magnesium Stearate.

INDICATION

Hypertension.

Prophylaxis of chronic stable angina pectoris.

Prinzmetal's (variant) angina when diagnosed by a cardiologist.

In hypertensive patients, Amlodipine has been used in combination with a thiazide diuretic, alpha blocker, beta-adrenoceptor blocking agent, or an angiotensin converting enzyme inhibitor. For angina, Amlodipine may be used as monotherapy or in combination with other antianginal drugs in patients with angina that is refractory to nitrates and/or adequate doses of beta blockers.

Amlodipine is well tolerated in patients with heart failure and a history of hypertension or ischaemic heart disease.

DOSAGE AND ADMINISTRATION

In adults: For both hypertension and angina the usual initial dose is 5mg Amlodipine once daily which may be increased to a maximum dose of 10mg depending on the individual patient's response.

No dose adjustment of Amlodipine is required upon concomitant administration of thiazide diuretics, beta blockers, and angiotensin-converting enzyme inhibitors.

Use in children: Children with hypertension from 6 years to 17 years of age. The recommended antihypertensive oral dose in paediatric patients ages 6-17 years is 2.5 mg once daily as a starting dose, up-titrated to 5 mg once daily if blood pressure goal is not achieved after 4 weeks. Doses in excess of 5 mg daily have not been studied in paediatric patients (see **Clinical Pharmacology Pharmacodynamic Properties and Pharmacokinetic Properties**). The effect of amlodipine on blood pressure in patients less than 6 years of age is not known.

The 2.5 mg dose cannot be obtained with Amlodipine tablets 5 mg as these tablets are not manufactured to break into two equal halves.

Use in the elderly: Amlodipine, used at similar doses in elderly or younger patients, is equally well tolerated. Therefore normal dosage regimens are recommended.

Patients with hepatic impairment: See **Special warnings and precautions** for use.

Patients with renal impairment: Changes in amlodipine plasma concentrations are not correlated with degree of renal impairment, therefore the normal dosage is recommended. Amlodipine is not dialysable.

CONTRAINDICATIONS

Amlodipine is contra-indicated in patients with a known sensitivity to dihydropyridines, amlodipine or any of the excipients.

Amlodipine should not be used in cardiogenic shock, clinically significant aortic stenosis, unstable angina (excluding Prinzmetal's angina).

Pregnancy and lactation

DRUG INTERACTIONS

Amlodipine has been safely administered with thiazide diuretics, alpha blockers, beta blockers, angiotensin-converting enzyme inhibitors, long-acting nitrates, sublingual glyceryl trinitrate, non-steroidal anti-inflammatory drugs, antibiotics, and oral hypoglycaemic drugs.

In vitro data from studies with human plasma, indicate that amlodipine has no effect on protein binding of digoxin, phenytoin, warfarin or indometacin.

Consumption of grapefruit/grapefruit juice should be avoided while taking Amlodipine. The intake of grapefruit juice may result in increased plasma amlodipine concentrations, which may enhance the blood pressure lowering effects of amlodipine. This interaction has been observed with other dihydropyridine calcium antagonists and represents a class effect.

Special Studies: Effect of other agents on amlodipine

Cimetidine: Co-administration of Amlodipine with cimetidine did not alter the pharmacokinetics of Amlodipine.

Sildenafil: When Amlodipine and sildenafil were used in combination, each agent independently exerted its own blood pressure lowering effect.

Special Studies: Effect of amlodipine on other agents

Atorvastatin: Co-administration of multiple 10mg doses of Amlodipine with 80mg of atorvastatin resulted in no significant change in the steady state pharmacokinetic parameters of atorvastatin.

Digoxin: Co-administration of Amlodipine with digoxin did not change serum digoxin levels or digoxin renal clearance in normal volunteers.

Warfarin: In healthy male volunteers, the co-administration of Amlodipine does not significantly alter the effect of warfarin on prothrombin response time. Co-administration of Amlodipine with warfarin did not change the warfarin prothrombin response time.

Ciclosporin: Pharmacokinetic studies with ciclosporin have demonstrated that Amlodipine does not significantly alter the pharmacokinetics of ciclosporin.

Drug/Laboratory test Interactions: None known.

WARNINGS AND PRECAUTIONS

Use in patients with Heart Failure: In a long-term, placebo controlled study (PRAISE-2) of Amlodipine in patients with NYHA III and IV heart failure of nonischaemic aetiology, amlodipine was associated with increased reports of pulmonary oedema despite no significant difference in the incidence of worsening heart failure as compared to placebo. See **Clinical Pharmacology "Pharmacodynamic Properties".**

Use in patients with impaired hepatic function: As with all calcium antagonists, amlodipine's half-life is prolonged in patients with impaired liver function and dosage recommendations have not been established. The drug should therefore be administered with caution in these patients.

There are no data to support the use of Amlodipine alone, during or within one month of a myocardial infarction.

The safety and efficacy of Amlodipine in hypertensive crisis has not been established.

PREGNANCY AND LACTATION

Although some dihydropyridine compounds have been found to be teratogenic in animals, data in the rat and rabbit for amlodipine provide no evidence for a teratogenic effect. There is, however, no clinical experience with the preparation in pregnancy or lactation. Accordingly, Amlodipine should not be administered during pregnancy, or lactation, or to women of childbearing potential unless effective contraception is used.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Clinical experience with Amlodipine indicates that therapy is unlikely to impair a patient's ability to drive or use machinery.

SIDE EFFECTS

Adverse events that have been reported in amlodipine trials are categorised below, according to system organ class and frequency. Frequencies are defined as: very common (>10%); common (>1%, <10%); uncommon (>0.1%, <1%); rare (>0.01%, <0.1%) and very rare (<0.01%).

Blood and the Lymphatic System Disorders	thrombocytopenia	Very Rare
Immune System Disorders	allergic reaction	Very Rare
Metabolism and Nutrition Disorders	hyperglycaemia	Very Rare
Psychiatric Disorders	insomnia, mood changes	Uncommon
Nervous System Disorders	somnolence, dizziness, headache	Common
	tremor, taste perversion, syncope, hypoaesthesia, paraesthesia	Uncommon
	peripheral neuropathy	Very Rare
Eye Disorders	visual disturbances	Uncommon
Ear and Labyrinth Disorders	tinnitus	Uncommon
Cardiac Disorders	palpitations	Common
	myocardial infarction, arrhythmia, ventricular tachycardia and atrial fibrillation)	Very Rare
Vascular Disorders	flushing	Common
	hypotension	Uncommon
	vasculitis	Very Rare
Respiratory, Thoracic and Mediastinal Disorders	dyspnoea, rhinitis	Uncommon
	coughing	Very Rare
Gastrointestinal Disorders	abdominal pain, nausea	Common
	vomiting, dyspepsia, altered bowel habits, dry mouth	Uncommon
	pancreatitis, gastritis, gingival hyperplasia	Very Rare
Hepato-biliary Disorders	hepatitis, jaundice and hepatic enzyme elevations (mostly consistent with cholestasis)	Very Rare
Skin and Subcutaneous Tissue Disorders	alopecia, purpura, skin discolouration, increased sweating, pruritus, rash	Uncommon
	angioedema, erythema multiforme, urticaria	Very Rare
Musculoskeletal and Connective Tissue Disorders	arthralgia, myalgia, muscle cramps, back pain	Uncommon
Renal and Urinary Disorders	micturition disorder, nocturia, increased urinary frequency	Uncommon

Size: 180x300 mm
Pharmacode: Front:7201 Back:7202
No,of colors: 01, Black
Die Cut:
Note: Pharmacode position and orientation will be changed as per folding dimension

Reproductive System and Breast Disorders	impotence, gynaecomastia	Uncommon
General Disorders and Administration Site Conditions	oedema, fatigue	Common
	chest pain, asthenia, pain, malaise	Uncommon
Investigations	Investigations weight increase, weight decrease	Uncommon

OVERDOSE

Available data suggest that gross overdosage could result in excessive peripheral vasodilatation and possibly reflex tachycardia. Marked and probably prolonged systemic hypotension up to and including shock with fatal outcome have been reported.

Administration of activated charcoal to healthy volunteers immediately or up to two hours after ingestion of amlodipine 10mg has been shown to significantly decrease amlodipine absorption. Gastric lavage may be worthwhile in some cases. Clinically significant hypotension due to Amlodipine overdosage calls for active cardiovascular support including frequent monitoring of cardiac and respiratory function, elevation of extremities, and attention to circulating fluid volume and urine output. A vasoconstrictor may be helpful in restoring vascular tone and blood pressure, provided that there is no contraindication to its use. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade. Since Amlodipine is highly protein-bound, dialysis is not likely to be of benefit.

CLINICAL PHARMACOLOGY

Pharmacodynamic Properties

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

The mechanism of the antihypertensive action of Amlodipine is due to a direct relaxant effect on vascular smooth muscle. The precise mechanism by which Amlodipine relieves angina has not been fully determined but Amlodipine reduces total ischaemic burden by the following two actions.

1) Amlodipine dilates peripheral arterioles and thus, reduces the total peripheral resistance (afterload) against which the heart works. Since the heart rate remains stable, this unloading of the heart reduces myocardial energy consumption and oxygen requirements.

2) The mechanism of action of Amlodipine also probably involves dilatation of the main coronary arteries and coronary arterioles, both in normal and ischaemic regions. This dilatation increases myocardial oxygen delivery in patients with coronary artery spasm (Prinzmetal's or variant angina).

In patients with hypertension, once daily dosing provides clinically significant reductions of blood pressure in both the supine and standing positions throughout the 24 hour interval. Due to the slow onset of action, acute hypotension is not a feature of Amlodipine administration.

In patients with angina, once daily administration of Amlodipine increases total exercise time, time to angina onset, and time to 1mm ST segment depression, and decreases both angina attack frequency and glyceryl trinitrate tablet consumption.

Amlodipine has not been associated with any adverse metabolic effects or changes in plasma lipids and is suitable for use in patients with asthma, diabetes, and gout.

Use in Patients with Heart Failure: Haemodynamic studies and exercise based controlled clinical trials in NYHA Class II-IV heart failure patients have shown that Amlodipine did not lead to clinicel deterioration as measured by exercise tolerance, left ventricular ejection fraction and clinical symptomatology.

A placebo controlled study (PRAISE) designed to evaluate patients in NYHA Class III-IV heart failure receiving digoxin, diuretics and ACE inhibitors has shown that Amlodipine did not lead to an increase in risk of mortality or combined mortality and morbidity with heart failure.

In a follow-up, long term, placebo controlled study (PRAISE-2) of Amlodipine in patients with NYHA III and IV heart failure without clinical symptoms or objective findings suggestive or underlying ischaemic disease, on stable doses of ACE inhibitors, digitalis, and diuretics, Amlodipine had no effect on total cardiovascular mortality. In this same population Amlodipine was associated with increased reports of pulmonary oedema despite no significant difference in the incidence of worsening heart failure as compared to placebo.

A randomized double-blind morbidity-mortality study called the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) was performed to compare newer drug therapies: amlodipine 2.5-10 mg/d (calcium channel blocker) or lisinopril 10-40 mg/d (ACE-inhibitor) as first-line therapies to that of the thiazide-diuretic, chlorthalidone 12.5-25 mg/d in mild to moderate hypertension."

A total of 33,357 hypertensive patients aged 55 or older were randomized and followed for a mean of 4.9 years. The patients had at least one additional CHD risk factor, including: previous myocerdial infarction or stroke (> 6 months prior to enrollment) or documentation of other atherosclerotic CVD (overall 51.5%), type 2 diabetes (36.1%), HDL-C < 35 mg/dL (11.6%), left ventricular hypertrophy diagnosed by electrocardiogram or echocardiography (20.9%), current cigarette smoking (21.9%).

The primary endpoint was a composite of fatal CHD or non-fatal myocardial infarction. There was no significant difference in the primary endpoint between amlodipine-based therapy and chlorthalidone-based therapy: RR 0.98 95% CI(0.90-1.07) p=0.65. Among Secondary Endpoints, the incidence of heart failure (component of a composite combined cardiovascular endpoint) was significantly higher in the amlodipine group as compared to the chlorthalidone group (10.2% % vs 7.7%, RR 1.38, 95% CI [1.25-1.52] p<0.001). However, there was no significant difference in all-cause mortality between amlodipine-based therapy and chlorthalidone-based therapy. RR 0.96 95% CI [0.89-1.02] p=0.20.

In a study involving 268 children aged 6-17 years with predominantly secondary hypertension, comparison of a 2.5mg dose, and 5.0mg dose of amlodipine with placebo, showed that both doses reduced Systolic Blood Pressure significantly more than placebo. The difference between the two doses was not statistically significant.

The long-term effects of amlodipine on growth, puberty and general development have not been studied. The long-term efficacy of amlodipine on therapy in childhood to reduce cardiovascular morbidity and mortality in adulthood have also not been established.

Pharmacokinetic Properties

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 circulating amlodipine is bound to plasma proteins.

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 the urine.

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.

A population PK study has been conducted in 74 hypertensive children aged from 12 months to 17 years (with 34 patients aged 6 to 12 years and 28 patients aged 13 to 17 years) receiving amlodipine between 1.25 and 20 mg given either once or twice daily. In children 6 to 12 years and in adolescents 13-17 years of age 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 6 years is limited.

HOW SUPPLIED

AMLO-H 5
Amlodipine Tablets 5 mg

Each uncoated tablet contains Amlodipine 5 mg (equivalent to 6.934 mg of Amlodipine Besilate)

White to off white round shaped, biconvex tablets debossed with 'J' on one side and '20' on the other side.

AMLO-H 10
Amlodipine Tablets 10 mg

Each uncoated tablet contains Amlodipine 10 mg (equivalent to 13.868 mg of Amlodipine Besilate)

White to off white round shaped, biconvex tablets debossed with 'J' on one side and '21' on the other side.

BLISTER PACK 10's Blister - Printad Aluminium foil - White opaque PVC/90 GSM PVdC
10's Blister - Printed Aluminium foil - Cold form foil

STORAGE: Store below 30°C and protect from moisture.

Manufactured by:
HETERO LABS LIMITED
Unit- V, TSIIC Formulation SEZ, S.No. 439, 440, 441 & 458,
Polepally Village, Jadcherla, Mahaboob Nagar – 509301,
Telangana State, INDIA.

Product Registration Holder:
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Jalan Kerinchi, Gerbang Kerinchi Lestari,
59200 Kuala Lumpur, Malaysia.

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