For the use only of a Registered Medical Practitioner

PRESCRIBING INFORMATION

VAMLO TABLETS
(Amlodipine Besilate Tablets)

COMPOSITION

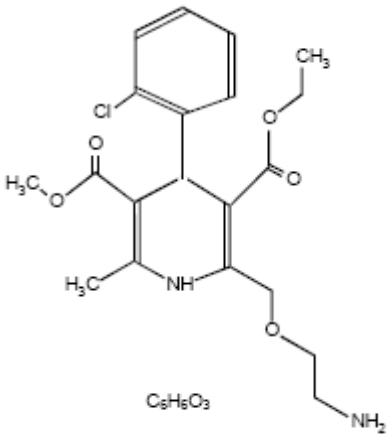
VAMLO 5
Each tablet contains:
Amlodipine Besilate BP equivalent to Amlodipine ……..……5 mg

VAMLO 10
Each tablet contains:
Amlodipine Besilate BP equivalent to Amlodipine ……..……10 mg

PRODUCT DESCRIPTION
5 mg White to off-white, flat, beveled edge, round, uncoated tablets with a score-line on one side.
Diameter : 8.0 mm

10 mg: White to off-white, flat, beveled edge, round, uncoated tablets with a score-line on one side.
Diameter : 10.5 mm

DESCRIPTION
VAMLO TABLETS contain besilate salt of amlodipine, which is a long-acting calcium channel blocker. Amlodipine besilate is chemically described as 3-ethyl-5-methyl (±)-2-[(2-aminoethoxy)methyl]4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate, monobenzenesulphonate. Its empirical formula is $C_{20}H_{25}CLN_2O_5 \bullet C_6H_6O_3S$ and the structural formula is:



AMLODIPINE BESILATE

PHARMACODYNAMIC AND PHARMACOKINETIC PROPERTIES

- Pharmacodynamics

Amlodipine besilate is a calcium ion influx inhibitor (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 ischemic 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 ischemic regions. This dilatation increases myocardial oxygen delivery in patients with coronary artery spasm (Prinzmetal's or variant angina) and blunts smoking induced coronary vasoconstriction.

- Pharmacokinetics

Absorption

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. Approximately 97.5% of circulating amlodipine is bound to plasma proteins. Absorption of amlodipine is unaffected by consumption of food.

Biotransformation/Elimination

The terminal plasma elimination half life is about 35-50 hours and is consistent with once daily dosing. Steady state plasma levels are reached after 7-8 days of consecutive 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 patients of this age group.

INDICATIONS / USAGE

Amlodipine is indicated for the first line treatment of hypertension and can be used as a sole agent to control blood pressure in the majority of patients. Patients not adequately controlled on a single anti-hypertensive agent may benefit from the addition of amlodipine, which has been used in combination with a thiazide diuretic, alpha blocker, beta-adrenoceptor blocking agent, or an angiotensin converting enzyme inhibitor.

Amlodipine is indicated for the first line treatment of myocardial ischemia, whether due to fixed obstruction (stable angina) and or vasospasm/vasoconstriction (Prinzmetal's or variant angina) of coronary vasculature. Amlodipine may be used where the clinical presentation suggests a possible vasospastic/ vasoconstrictive component but where vasospasm/vasoconstriction has not been confirmed. Amlodipine may be used alone 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.

DOSE AND METHOD OF ADMINISTRATION

For both hypertension and angina the usual initial dose is 5 mg amlodipine once daily which may be increased to a maximum dose of 10 mg 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.

Adjust dosage according to blood pressure goals. In general, wait 7 to 14 days between titration steps. Titrate more rapidly, however, if clinically warranted, provided the patient is assessed frequently.

Use in the Elderly
Amlodipine, used at similar doses in elderly or younger patients, is equally well tolerated. Normal dosage regimens are recommended in the elderly, but increase of the dosage should take place with care.

Use in Children
Safety and effectiveness of amlodipine in children have not been established.

Use in Patients with Impaired Hepatic Function
Dosage recommendations have not been established in patients with mild to moderate hepatic impairment; therefore dose selection should be cautious and should start at the lower end of the dosing range. The pharmacokinetics of amlodipine has not been studied in severe hepatic impairment. Amlodipine should be initiated at the lowest dose and titrated slowly in patients with severe hepatic impairment.

Use in Renal Failure
Amlodipine may be used in such patients at normal doses. Changes in amlodipine plasma concentrations are not correlated with degree of renal impairment. Amlodipine is not dialyzable.

ROUTE OF ADMINISTRATION : Oral

CONTRAINDICATIONS

In patients with a known sensitivity to dihydropyridines, amlodipine or any of the excipients.

WARNINGS AND PRECAUTIONS

Use in Patients with Heart Failure
Amlodipine was associated with increased reports of pulmonary oedema despite no significant difference in the incidence of worsening heart failure as compared to placebo.

Use in Patients with Impaired Hepatic Function

The half-life of amlodipine is prolonged and AUC values are higher in patients with impaired liver function; dosage recommendations have not been established. Amlodipine should therefore be initiated at the lower end of the dosing range and caution should be used, both on initial treatment and when increasing the dose. Slow dose titration and careful monitoring may be required in patients with severe hepatic impairment.

Effect 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.

DRUG INTERACTIONS

Amlodipine has been safely administered with thiazide diuretics, alpha blockers, beta blockers, angiotensin-converting enzyme inhibitors, long-acting nitrates, sublingual nitroglycerine , non-steroidal anti-inflammatory drugs, antibiotics, and oral hypoglycaemic drugs. Amlodipine has been no effect on protein binding of the drugs tested (digoxin, phenytoin, warfarin or indomethacin). Administration of amlodipine with grapefruit or grapefruit juice is not recommended as bioavailability may be increased in some patients resulting in increased blood pressure lowering effects.

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.

Aluminum/ Magnesium (Antacid): Co-administration of an aluminium /magnesium antacid with single dose of amlodipine had no significant effect on the pharmacokinetics of amlodipine.

CYP3A4 Inhibitors: It cannot be ruled out that strong inhibitors of CYP3A4 (e.g. ketoconazole, itraconazole, ritonavir) may increase the plasma concentrations of amlodipine to a greater extent than diltiazem. Amlodipine should be used with caution together with CYP3A4 inhibitors; however no adverse events attributable to such interaction have been reported.

CYP3A4 Inducers: There is no data available regarding the effect of CYP3A4 inducers on amlodipine. The concomitant use of CYP3A4 inducers (e.g. rifampicin, hypericum perforatum) may give a lower plasma concentration of amlodipine. Amlodipine should be used with caution together with CYP3A4 inducers.

Effect of amlodipine on other agents

Atorvastatin: Co-administration of amlodipine with 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.

Warfarin: Co-administration of amlodipine with warfarin did not change the warfarin prothrombin response time.

Cyclosporin: Amlodipine does not significantly alter the pharmacokinetics of cyclosporin.

Ethanol (alcohol): Amlodipine had no significant effect on pharmacokinetics of ethanol.

SIDE EFFECTS/ ADVERSE REACTIONS

Amlodipine is well tolerated. The most commonly observed side effects were:

System Organ Class	Undesirable Effects
Nervous System Disorders	Headache, dizziness, somnolence
Cardiac Disorders	Palpitations
Vascular Disorders	Flushing
Gastrointestinal Disorders	Abdominal pain, nausea
General Disorders and Administration Site Conditions	Oedema, fatigue

Less commonly observed side effects in marketing experience include:

System Organ Class	Undesirable Effects
Blood and Lymphatic System Disorders	Leucopenia, thrombocytopenia
Metabolism and Nutrition Disorders	hyperglycemia
Psychiatric Disorders	Insomnia, mood changes
Nervous System Disorders	Hypertonia, hypoesthesia/ paraesthesia peripheral neuropathy, syncope, taste perversion, tremor
Eye Disorders	Visual disturbances
Ear and Labyrinth Disorders	Tinnitus
Vascular Disorders	Hypotension, vasculitis
Respiratory, Thoracic and Mediastinal Disorders	Cough, dyspnea, rhinitis
Gastrointestinal Disorders	Altered bowel habits, dry mouth, dyspepsia (including gastritis), gingival hyperplasia, pancreatitis, vomiting
Skin and Subcutaneous Disorders	Alopecia, increased sweating, purpura, skin discoloration, urticaria
Musculoskeletal and Connective Tissue Disorders	Arthralgia, back pain, muscle cramps, myalgia
Renal and Urinary Disorders	Increased urinary frequency, micturition disorder, nocturia
Reproductive System and Breast Disorders	Gynecomastia, impotence
General Disorders and Administration Site	Asthenia, malaise, pain

Rarely, allergic reaction including pruritus, rash, angioedema, and erythema multiforme. Hepatitis, jaundice and hepatic enzyme elevations have also been reported very infrequently (mostly consistent with cholestasis).

As with other calcium channel blockers the following adverse events have been rarely reported and cannot be distinguished from the natural history of the underlying disease: myocardial infarction, arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation) and chest pain.

USE IN SPECIAL POPULATIONS

- Pregnancy and Lactation

Safety of amlodipine in human pregnancy or lactation has not been established. Amlodipine does not demonstrate toxicity in reported animal reproductive studies other than to delay parturition or prolong labour in rats at dose level fifty times the maximum recommended dose in humans. Accordingly, use in pregnancy is only recommended when there is no safer alternative and when the disease itself carries greater risk for the mother and fetus.

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

OVERDOSE

Overdosage of amlodipine 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 10 mg 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.

STORAGE

Store below 30^0C, protected from light & moisture.

KEEP ALL MEDICINES OUT OF REACH OF CHILDREN

PACKING

Blister strip of 3 x 10's and 10 x 10's

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Product Registration Holder / Manufactured by:
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