Amlodipine besilate

Amvasc® BE

5 mg & 10 mg Tablet

Calcium Channel Blocker

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FORMULATION
Each tablet contains:
Amlodipine (as besilate) …….. 5 mg or 10 mg

PRODUCT DESCRIPTION
Amlodipine besilate (Amvasc® BE) 5 mg Tablet: White, round tablet, 5/16" in diameter, beveled-edged, with bisection on one side
Amlodipine besilate (Amvasc® BE) 10 mg Tablet: White, round plain tablet, 3/8" in diameter, bisected on one side

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS
Amlodipine, a dihydropyridine calcium antagonist (slow channel blocker or calcium ion antagonist), inhibits the transmembrane influx of calcium ions into cardiac muscle and vascular smooth muscle. Its antihypertensive action is due to a direct relaxant effect on vascular smooth muscle resulting in decreased peripheral vascular resistance and blood pressure.
Amlodipine's exact mechanism in relieving angina has not been fully established; however, amlodipine decreases total ischemic burden by (1) dilating peripheral arterioles thereby reducing total peripheral resistance (afterload) against which the heart works. The unloading of the heart decreases myocardial energy consumption and oxygen requirements as the heart rate remains stable; and (2) dilating the main coronary arteries and arterioles, both in normal and ischemic areas. This dilatation increases myocardial oxygen delivery in patients with coronary artery spasm (Prinzmetal's or variant angina).

PHARMACOKINETICS
After oral administration of therapeutic doses of amlodipine, peak plasma concentrations are reached between 6 and 12 hours. Amlodipine's absolute bioavailability is between 64 and 90%; its bioavailability is unaffected by food. Amlodipine's volume of distribution is about 20 L/kg.
About 90% of amlodipine is converted to inactive metabolites via hepatic metabolism with 10% of the parent compound and 60% of the metabolites excreted in the urine. Studies have shown that about 93% of the circulating drug is bound to plasma proteins in hypertensive patients. Plasma elimination is biphasic with a terminal elimination half-life of 30 to 50 hours. Steady state plasma amlodipine concentrations are reached after 7 to 8 days of consecutive dosing.
The pharmacokinetics of amlodipine is not significantly influenced by renal impairment. Thus, the usual initial dose may be given to patients with renal failure.
Amlodipine's clearance is decreased and the AUC increased (by 40 to 60%) in elderly patients and patients with hepatic impairment. Plasma amlodipine elimination half-life ($t_{1/2}$) is prolonged (56 hours) in patients with hepatic impairment. Thus, a lower initial dose may be given in these patients. A comparable increase in AUC was seen in patients with moderate to severe heart failure.

INDICATIONS
Treatment of hypertension and prophylaxis of angina.

DOSAGE AND ADMINISTRATION
Usual Oral Adult Dose: 5 mg once daily
Maximum Dose: 10 mg once daily
In hypertension, the usual dose is 5 mg once daily, increased if necessary, to 10 mg once daily. Similar doses are given in the treatment of stable angina and Prinzmetal's angina
Recommended dose for chronic stable or vasospastic angina: 5-10 mg once daily, with the lower dose (5 mg) suggested in the elderly and in patients with hepatic insufficiency.
Recommended dose for patients with coronary artery disease: 5-10 mg once daily
Pediatric Dose: The effective antihypertensive dose in children 6-17 years old is 2.5mg to 5 mg once daily.
Adjust dosage according to patient's age and symptom.
Or as prescribed by the physician.

CONTRAINDICATIONS
- Hypersensitivity to amlodipine besilate, dihydropyridines, or any component of the product
- Severe hypotension
- Shock (including cardiogenic shock)
- Obstruction of the outflow tract of the left ventricle (e.g., high grade aortic stenosis)
- Hemodynamically unstable heart failure after myocardial infarction

WARNINGS AND PRECAUTIONS
Increased Angina or Myocardial Infarction: **A**fter initiating or increasing the dose of amlodipine, particularly in patients with severe obstructive coronary artery disease, worsening angina and acute myocardial infarction may develop.
Hypotension: Symptomatic hypotension is possible, particularly in patients with severe aortic stenosis. However, acute hypotension is unlikely because of the gradual onset of action of amlodipine.
Heart Failure: In general, calcium channel blockers should be used with caution in patients with heart failure. In a controlled trial on amlodipine in patients with severe heart failure (NYHA III and IV), amlodipine was associated with increased reports of pulmonary edema.
Hepatic Impairment: Amlodipine should be used with caution and in reduced dosage in patients with hepatic impairment. Titrate slowly in patients with severe hepatic impairment.
Effects on ability to drive and use machine
Amlodipine may have minor or moderate influence on the ability to drive and use machines. If patients taking amlodipine suffer from dizziness, headache, fatigue or nausea, the ability to react may be impaired. Caution is recommended at the start of treatment.

INTERACTIONS WITH OTHER MEDICAMENTS
Cimetidine, antacid (aluminum/magnesium hydroxide), or sildenafil: No significant effect on the pharmacokinetics of amlodipine
Grapefruit Juice: Coadministration may increase the bioavailability of amlodipine resulting in increased blood pressure lowering effects. Thus, grapefruit should not be taken with amlodipine.
Digoxin: Concomitant use did not change the serum digoxin levels or digoxin renal clearance in normal volunteers
Ethanol (alcohol): No significant effect on the pharmacokinetics of ethanol
Warfarin: Concomitant use did not change the warfarin prothrombin response time
Atorvastatin: No significant change in steady state pharmacokinetic parameters of atorvastatin
Simvastatin: Concomitant use of multiple doses of amlodipine (10 mg) with higher doses of simvastatin (80 mg) resulted in increased exposure to simvastatin. Do not exceed doses of simvastatin greater than 20 mg daily in patients on amlodipine.
Cytochrome P450 3A4 (CYP3A4) Inhibitors: Concomitant use of amlodipine with strong or moderate CYP3A4 inhibitors [protease inhibitors (e.g., ritonavir), azole antifungals (e.g., ketoconazole, itraconazole), macrolides (e.g., erythromycin, clarithromycin), verapamil or diltiazem] may increase the plasma concentrations of amlodipine to a greater extent. The clinical effects of these pharmacokinetic variations may be more pronounced in the elderly. Clinical monitoring and dose adjustment may therefore be required.
CYP3A4 Inducers: There is no data available regarding the effect of CYP3A4 inducers on amlodipine. Concomitant use of CYP3A4 inducers (e.g., rifampicin, St. John's Wort) may result in lower plasma concentrations of amlodipine. Amlodipine should be used with caution when administered with CYP3A4 inducers.
Ciclosporin: An increase in trough ciclosporin levels was observed in renal transplant patients when concomitantly administered with amlodipine
Tacrolimus: Coadministration may increase blood levels of tacrolimus. Monitor blood levels and adjust dosage of tacrolimus as appropriate to avoid toxicity

STATEMENT ON USAGE FOR HIGH RISK GROUPS
Pregnancy: Pregnancy Category C. No adequate or well-controlled studies have been done in humans. Amlodipine should only be used during pregnancy if the potential benefit justifies the potential risk to the fetus.
Lactation: It is not known whether amlodipine is excreted in human milk. Thus, breastfeeding is not recommended during amlodipine administration.
Elderly: Observe caution in amlodipine dose selection for an elderly. Elderly patients are more likely to experience delayed clearance of amlodipine and can be at greater risk for toxicity.
Children: The effect of amlodipine on blood pressure in children < 6 years old has not been established.

UNDESIRABLE EFFECTS
The most commonly reported adverse reactions during treatment with amlodipine are somnolence, dizziness, headache, palpitations, flushing, abdominal pain, nausea, ankle swelling, edema and fatigue.
Body as a Whole: Asthenia, chest pain, edema/swelling, fatigue, malaise, pain, peripheral edema, rigors
Cardiovascular: Arrhythmia (including ventricular tachycardia and atrial fibrillation), bradycardia, flushing, hypotension, hot flushes, myocardial infarction, palpitation, peripheral ischemia, syncope, tachycardia, vasculitis
Gastrointestinal: Abdominal pain, altered bowel habits, anorexia, constipation, diarrhea, dry mouth, dyspepsia, dysphagia, flatulence, gastritis, gingival hyperplasia, nausea, pancreatitis, vomiting
Genitourinary: Gynecomastia, impotence, micturition frequency, micturition disorder, nocturia, sexual dysfunction
Hematologic: Thrombocytopenia, leukopenia
Hepatobiliary: Hepatic enzyme elevations (mostly consistent with cholestasis), hepatitis, jaundice
Hypersensitivity: Allergic reactions
Metabolic: Hyperglycemia, thirst, weight increase/decrease
Musculoskeletal: Ankle swelling, arthralgia, arthrosis, back pain, muscle cramps, myalgia
Nervous System: Abnormal dreams, anxiety, confusion, depersonalization, dysgeusia, depression, dizziness, extrapyramidal disorder, headache, hypertonia, hypoesthesia, insomnia, mood changes, nervousness, paresthesia, peripheral neuropathy, somnolence, tremor, vertigo
Respiratory: Cough, dyspnea, epistaxis, rhinitis
Skin: Alopecia, angioedema, exanthema, erythema multiforme, exfoliative dermatitis, hyperhidrosis, purpura, pruritus, photosensitivity, rash, rash erythematous, rash maculopapular, skin discoloration, urticaria, Stevens-Johnson syndrome (very rare), Quincke edema (very rare)
Special senses: Conjunctivitis, diplopia, eye pain, tinnitus, abnormal vision, visual disturbances

OVERDOSE AND TREATMENT
Overdosage might be expected to cause excessive peripheral vasodilation with marked hypotension and possibly a reflex tachycardia.
Institute active cardiac and respiratory monitoring during massive overdose. Frequent blood pressure measurements are necessary. Initiate cardiovascular support (i.e., elevation of extremities, judicious administration of fluids) if hypotension occurs. If hypotension remains unresponsive to these conservative measures, administration of vasopressors such as phenylephrine should be considered with attention to circulation volume and urine output. Intravenous calcium gluconate may help reverse the effects of calcium entry blockade. Hemodialysis is not likely to be of benefit since amlodipine is highly protein bound.

CAUTION
Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

ADVERSE DRUG REACTION REPORTING STATEMENT
For suspected adverse drug reaction, seek medical attention immediately and report to the FDA at www.fda.gov.ph **AND** Unilab at (+632) 864-5221 (UNILAB-1) or productsafety@unilab.com.ph. By reporting undesirable effects, you can help provide more information on the safety of this medicine.

STORAGE CONDITIONS
Store at temperatures not exceeding 30°C.
Keep the product out of sight and reach of children.

AVAILABILITY
Amlodipine besilate (Amvasc® BE) 5 mg Tablet, box of 50's (in flex foil) (DRP-1202)
Amlodipine besilate (Amvasc® BE) 10 mg Tablet, box of 50's (in flex foil) (DRP-1195)

Manufactured by AMHERST LABORATORIES, INC.
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