Amcab®

(Amlodipine Besilate)

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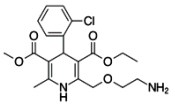
DESCRIPTION:

AMCAB is the besilate salt of amlodipine, a long-acting calcium channel blocker. Its empirical formula is C20H25CIN2O5•C6H6O3S, and its structural formula is:



AMCAB (amlodipine besilate) Tablets are equivalent to 2.5, 5, and 10 mg of amlodipine for oral administration.

CLINICAL PHARMACOLOGY:

Mechanism of Action:

Amlodipine is a dihydropyridine calcium antagonist (calcium ion antagonist or slow-channel blocker) that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. Experimental data suggest that amlodipine binds to both dihydropyridine and nondihydropyridine 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 vascularsmooth 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.

The precise mechanisms by which amlodipine relieves angina have not been fully delineated, but are thought to include the following: Exertional Angina: In patients with exertional angina, AMCAB reduces the total peripheral resistance (afterload) against which the heart works and reduces the rate pressure product, and thus myocardial oxygen demand, at any given level of exercise.

Vasospastic Angina:AMCAB has been demonstrated to block constriction and restore blood flow in coronary arteries and arterioles in response to calcium, potassium epinephrine, serotonin, and thromboxane A2 analog in experimental animal models and in human coronary vessels in vitro. This inhibition of coronary spasm is responsible for the effectiveness of AMCAB in vasospastic (Prinzmetal's or variant) angina.

Pharmacodynamics:

Hemodynamics: Following administration of therapeutic doses to patients with hypertension, Amlodipine (AMCAB) 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. Although the acute intravenous administration of amlodipine decreases arterial blood pressure and increases heart rate in hemodynamic studies of patients with chronic stable angina, chronic oral administration of amlodipine in clinical trials did not lead to clinically significant changes in heart rate or blood pressures in normotensive patients with angina.

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 (AMCAB) is also correlated with the height of pretreatment 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 glomerular filtration rate and effective renal plasma flow without change in filtration fraction or proteinuria.

Electrophysiologic Effects: AMCAB does not change sinoatrial nodal function or atrioventricular conduction in intact animals or man. In patients with chronic stable angina, intravenous administration of 10 mg did not significantly alter A-H and H-V conduction and sinus node recovery time after pacing. Similar results were obtained in patients receiving Amlodipine and concomitant beta-blockers. In clinical studies in which Amlodipine was administered in combination with beta-blockers to patients with either hypertension or angina, no adverse effects on electrocardiographic parameters were observed.

Pharmacokinetics & Metabolism:

After oral administration of therapeutic doses of AMCAB, absorption produces peak plasma concentrations between 6 and 12 hours. Absolute bioavailability has been estimated to be between 64 and 90%. The bioavailability of AMCAB 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 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.

INDICATIONS:

Hypertension: AMCAB is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents.

Coronary Artery Disease (CAD)-

Chronic Stable Angina: AMCAB is indicated for the symptomatic treatment of chronic stable angina. AMCAB may be used alone or in combination with other antianginal agents.

Vasospastic Angina (Prinzmetal's or Variant Angina): AMCAB is indicated for the treatment of confirmed or suspected vasospastic angina. AMCAB may be used as monotherapy or in combination with other antianginal agents.

Angiographically Documented CAD: In patients with recently documented CAD by angiography and without heart failure or an ejection fraction <40%, AMCAB is indicated to reduce the risk of hospitalization due to angina and to reduce the risk of a coronary revascularization procedure.

DOSAGE & ADMINISTRATION:

Adults: The usual initial antihypertensive oral dose of AMCAB is 5 mg once daily with a maximum dose of 10 mg once daily.Small, fragile, or elderly patients, or patients with hepatic insufficiency may be started on 2.5 mg once daily and this dose may be used when adding AMCAB to other antihypertensive therapy.

Adjust dosage according to each patient's need. In general, titration should proceed over 7 to 14 days so that the physician can fully assess the patient's response to each dose level. Titration may proceed more rapidly, however, if clinically warranted, provided the patient is assessed frequently.

The recommended dose for chronic stable or vasospastic angina is 5–10 mg, with the lower dose suggested in the elderly and in patients with hepatic insufficiency. Most patients will require 10 mg for adequate effect.

The recommended dose range for patients with coronary artery disease is 5–10 mg once daily. In clinical studies, the majority of patients required 10 mg.

Children: The effective antihypertensive oral dose in pediatric patients ages 6–17 years is 2.5 mg to 5 mg once daily. Doses in excess of 5 mg daily have not been studied in pediatric patients.

ADVERSE DRUG REACTIONS:

Cardiovascular: flushing, palpitation | Central nervous system: Headache, fatigue | Dermatologic: Rashes | Gastrointestinal:nausea,abdominal pain.

CONTRAINDICATIONS:

SPANBEC is contraindicated in patients with known sensitivity to amlodipine.

DRUG INTERACTIONS:

In Vitro Data: In vitro data indicate that Amlodipine (AMCAB) has no effect on the human plasma protein binding of digoxin, phenytoin, warfarin, and indomethacin.

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

Grapefruit Juice: Co-administration of 240 mL of grapefruit juice with a single oral dose of amlodipine 10 mg in 20 healthy volunteers had no significant effect on the pharmacokinetics of amlodipine.

Magnesium and Aluminum Hydroxide Antacid: Co-administration of a magnesium and aluminum hydroxide antacid with a single dose of Amlodipine(AMCAB) had no significant effect on the pharmacokinetics of AMCAB.

Sildenafil: A single 100 mg dose of sildenafil in subjects with essential hypertension had no effect on the pharmacokinetic parameters of AMCAB. When Amlodipine (AMCAB) and sildenafil were used in combination, each agent independently exerted its own blood pressure lowering effect.

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

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

Ethanol (Alcohol): Single and multiple 10 mg doses of AMCAB had no significant effect on the pharmacokinetics of ethanol.

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

CYP3A4 Inhibitors: Co-administration of a 180 mg daily dose of diltiazem with 5 mg amlodipine in elderly hypertensive patients resulted in a 60% increase in amlodipine systemic exposure. Erythromycin co-administration in healthy volunteers did not significantly change amlodipine systemic exposure. However, strong inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole, ritonavir) may increase the plasma concentrations of amlodipine to a greater extent. Monitor for symptoms of hypotension and edema when amlodipine is co-administered with CYP3A4 inhibitors.

CYP3A4 Inducers: No information is available on the quantitative effects of CYP3A4 inducers on amlodipine. Blood pressure should be closely monitored when Amlodipine is co-administered with CYP3A4 inducers.

Drug/Laboratory Test Interactions: None known.

SPECIAL PRECAUTIONS:

Hypotension: Symptomatic hypotension is possible, particularly in patients with severe aortic stenosis. Because of the gradual onset of action, acute hypotension is unlikely.

Increased Angina or Myocardial Infarction: Worsening angina and acute myocardial infarction can develop after starting or increasing the dose of AMCAB, particularly in patients with severe obstructive coronary artery disease.

Beta-Blocker Withdrawal: AMCAB is not a beta-blocker and therefore gives no protection against the dangers of abrupt beta-blocker withdrawal; any such withdrawal should be by gradual reduction of the dose of beta-blocker.

Patients with Hepatic Failure: Because AMCAB is extensively metabolized by the liver and the plasma elimination half-life (t 1/2) is 56 hours in patients with impaired hepatic function, titrate slowly when administering AMCAB to patients with severe hepatic impairment.

USE IN SPECIAL POPULATION:

Pregnancy: Pregnancy Category C – There are no adequate and well-controlled studies in pregnant women. Amlodipine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: 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 AMCAB is administered.

Pediatric Use: Effect of AMCAB on blood pressure in patients less than 6 years of age is not known.

Geriatric Use: Reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually startingat the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. Elderly patients have decreased clearance of amlodipine with a resulting increase of AUC of approximately 40–60%, and a lower initial dose may be required.

OVERDOSE:

Overdosage might be expected to cause excessive peripheral vasodilation with marked hypotension and possibly a reflex tachycardia. Single oral doses of amlodipine maleate equivalent to 40 mg amlodipine/kg and 100 mg amlodipine/kg in mice and rats, respectively, caused deaths. Single oral amlodipine maleate doses equivalent to 4 or more mg amlodipine/kg or higher in dogs (11 or more times the maximum recommended human dose on a mg/m2 basis) caused a marked peripheral vasodilation and hypotension.

If massive overdose should occur, initiate active cardiac and respiratory monitoring. Frequent blood pressure measurements are essential. Should hypotension occur, provide cardiovascular support including elevation of the extremities and the judicious administration of fluids. If hypotension remains unresponsive to these conservative measures, consider administration of vasopressors (such as phenylephrine) with attention to circulating volume and urine output. As AMCAB is highly protein bound, hemodialysis is not likely to be of benefit.

PRESENTATION:

AMCAB-2.5:

- Each uncoated tablet contains: Amlodipine Besilate equivalent to Amlodipine 2.5 mg.
  Packaging: 30 Tablets X 5 Blisters

AMCAB-5:

- Each uncoated tablet contains: Amlodipine Besilate equivalent to Amlodipine 5 mg.
  Packaging: 30 Tablets X 5 Blisters

AMCAB-10:

- Each uncoated tablet contains: Amlodipine Besilate equivalent to Amlodipine 10 mg.
  Packaging: 30 Tablets X 5 Blisters

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