AMLODIPINE besilate HYDROCHLOROTHIAZIDE

Amvasc® Plus

5 mg/12.5 mg and 10 mg/12.5 mg Tablet

CALCIUM CHANNEL BLOCKER / DIURETIC

Rx

FORMULATIONS

Each tablet contains:

Amlodipine ..... 5 mg
(Equivalent to Amlodipine besilate 6.934 mg)
Hydrochlorothiazide..... 12.5 mg
or
Amlodipine ..... 10 mg
(Equivalent to Amlodipine besilate 13.868 mg)
Hydrochlorothiazide..... 12.5 mg

PRODUCT DESCRIPTION

Amlodipine+ HCTZ (Amvasc® Plus) 5mg/12.5mg Tablet - White, round tablet, 5/16" in diameter, bevel-edged, bisected on one side and plain on the other side

Amlodipine+ HCTZ (Amvasc® Plus) 10mg/12.5mg Tablet - White, round tablet, 3/8" in diameter, bevel-edged, bisected on one side and plain on the other side

PHARMACODYNAMICS / MECHANISM OF ACTION

Amlodipine

Amlodipine is a dihydropyridine calcium antagonist 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 and vascular smooth muscles are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels.

Amlodipine inhibits calcium ion influx across cell membrane selectively, with a greater effect on vascular smooth 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 dissolution 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 a decrease in blood pressure.

Hydrochlorothiazide

Hydrochlorothiazide (HCTZ), a thiazide diuretic, increases the excretion of water by inhibiting the reabsorption of sodium and chloride ions at the distal renal tubule. The excretion of potassium and magnesium is also increased while the elimination of calcium and uric acid is decreased. Thiazide diuretics usually do not affect the normal blood pressure. When chronically administered, thiazide diuretics decrease peripheral vascular resistance. The exact mechanism responsible for lowered peripheral resistance is not known, however, excretion of urinary sodium by the kidneys is required to achieve blood pressure reduction.

Indirectly, the diuretic action of HCTZ reduces plasma volume, with consequent increases in plasma renin activity, aldosterone secretion, urinary potassium loss, and decrease in serum potassium.

Diuresis begins with two hours, peaks in about four hours and lasts about 6 to 12 hours after oral administration of HCTZ.

PHARMACOKINETICS

Amlodipine

After oral administration of therapeutic doses of amlodipine, peak plasma concentrations are reached between 6 and 12 hours. Absolute bioavailability has been estimated to be between 64 and 90%. The volume of distribution is approximately 20 L/kg. Amlodipine's bioavailability is not altered by the presence of food.

Amlodipine is extensively (about 90%) converted to inactive metabolite via hepatic metabolism with 10% of the parent compound and 60% of the metabolite excreted in the urine. 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 to 50 hours. Steady state plasma levels of amlodipine are reached after 7 to 8 days of consecutive dosing.

The pharmacokinetics of amlodipine is 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%; a lower initial dose may be required in these patients. A similar increase in AUC was observed in patients with moderate to severe heart failure.

Hydrochlorothiazide

HCTZ is well absorbed from the gastrointestinal tract. Oral bioavailability is approximately 65 – 75%. After oral administration of HCTZ at doses of 12.5 to 100 mg, peak plasma concentrations of 70 to 490 ng/mL are observed within 1 to 5 hours of dosing.

Approximately 40 – 60% of the drug is bound to plasma proteins. The drug crosses the placenta, but not the blood-brain barrier and is distributed in breast milk. It appears to be preferentially bound to red blood cells.

HCTZ is not metabolized but is eliminated rapidly as unchanged drug in the urine. HCTZ's elimination half-life ranged from 5.6 to 15 hours when plasma levels were followed for at least 24 hours. At least 61% of the oral dose is eliminated unchanged within 24 hours. Increased HCTZ plasma concentrations and a prolonged elimination half-life have been reported in patients with renal impairment.

INDICATION

Hypertension

DOSAGE AND ADMINISTRATION

Usual Recommended Oral Dose: 1 tablet once daily;
Dose may be increased to amlodipine 10 mg + HCTZ 12.5 mg tablet once daily depending on the individual patient's response.

Or, as prescribed by a physician.

CONTRAINDICATIONS

- Hypersensitivity to amlodipine besilate, hydrochlorothiazide, other sulfonamide derivatives, or to any component in this product.
- Advanced aortic stenosis because amlodipine can worsen the abnormal valve pressure gradient associated with this condition.
- Severe hepatic impairment and/or cholestasis
- Anuria and renal impairment
- Gout and/or hyperuricemia
- Pregnant women, women of childbearing potential or breastfeeding mothers
- Patients with known history of cardiogenic shock

WARNINGS AND PRECAUTIONS

Amlodipine

- **General Precaution:** Since the vasodilation induced by amlodipine is gradual in onset, acute hypotension has rarely been reported after oral use. However, as with any other peripheral vasodilator, caution should be exercised when administering amlodipine, particularly in patients with severe aortic stenosis.
- **Increased Angina and/or Myocardial Infarction:** Rarely, patients particularly those with severe obstructive coronary disease, have developed documented 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. The mechanism of this effect has not been elucidated.
- **Use in Patients with 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 NYHA III and IV heart failure of nonischemic etiology, amlodipine was associated with increased reports of pulmonary edema despite no significant difference in the incidence of worsening heart failure.
- **Beta-Blocker Withdrawal:** Amlodipine 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:** Use with caution in patients with hepatic disease. The amlodipine plasma elimination half-life ($t_{1/2}$) is prolonged (56 hours) in patients with hepatic disease and dosage adjustment is recommended.

Hydrochlorothiazide

- **Hypotension and Fluid/Electrolyte Imbalance:** As with all antihypertensive therapy, symptomatic hypotension may occur in some patients. Patients should be observed for clinical signs of fluid or electrolyte imbalance (e.g., volume depletion, hyponatremia, hypochloremic alkalosis, hypomagnesemia, or hypokalemia) which may occur particularly during intercurrent diarrhea or vomiting. Serum electrolytes should be monitored regularly. Signs and symptoms of fluid and electrolyte imbalance include dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, confusion, seizures, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances including nausea and vomiting.
  Hypokalemia may develop, particularly with brisk diuresis, when liver cirrhosis is present, or after prolonged therapy. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia may cause cardiac arrhythmia and may also sensitize or exaggerate the response of the heart to the toxic effects of digitalis (e.g., increased ventricular irritability).
  Although any chloride deficit is generally mild and usually does not require specific treatment, except under extraordinary situations (e.g., liver disease or renal disease), chloride replacement may be required in the treatment of metabolic alkalosis.
  Dilutional hyponatremia may be seen in edematous patients in hot weather. Appropriate treatment is water restriction rather than administration of salt, except in rare instances when the hyponatremia is life-threatening. Appropriate replacement therapy is the treatment of choice in actual salt depletion.
- **Renal Disease:** Use with caution in patients with severe renal disease because thiazides may precipitate azotemia.
- **Hepatic Disease:** Use with caution in patients with hepatic disease or progressive liver disease since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.
- **Hypersensitivity Reaction:** Hypersensitivity reactions to HCTZ may occur in patients with or without a history of allergy or bronchial asthma, but are more likely in patients with such a history. As a sulfonamide derivative, HCTZ can cause skin rashes and blood dyscrasias.
- **Systemic Lupus Erythematosus:** Exacerbation or activation of systemic lupus erythematosus has been associated with the use of thiazide diuretics.
- **Metabolic and Endocrine Effects:** Thiazide therapy may impair glucose tolerance. Dosage adjustment of antidiabetic agents, including insulin, may be required.
  Thiazides may decrease urinary calcium excretion and may cause intermittent and slight elevation of serum calcium. Marked hypercalcemia may be evidence of hidden hyperparathyroidism. Discontinue thiazides before taking parathyroid function test.
  Thiazide diuretic therapy may increase cholesterol and triglyceride levels. Hyperuricemia may occur or acute gout may be precipitated in certain patients taking thiazide therapy.
  Thiazides have been reported to increase the urinary excretion of magnesium. This may result in hypomagnesemia.

DRUG INTERACTIONS

Amlodipine besilate:

- ***Concomitant use of amlodipine with cimetidine, grapefruit juice, antacid (Aluminum/ Magnesium Hydroxide), or sildenafil*** had no significant effect on the pharmacokinetics of amlodipine.
- ***Atorvastatin:*** Concomitant use resulted in no significant change in steady state pharmacokinetic parameters of atorvastatin.
- ***Ciclosporin:*** Amlodipine does not significantly alter the pharmacokinetics of ciclosporin.
- ***Digoxin:*** Concomitant use did not change the serum digoxin levels or digoxin renal clearance in normal volunteers.
- ***Ethanol (Alcohol):*** Concomitant use had no significant effect on the pharmacokinetics of ethanol.
- ***Warfarin:*** concomitant use did not change the warfarin prothrombin response time.

Hydrochlorothiazide:

- ***Alcohol, barbiturates, or narcotics:*** Potentiation of orthostatic hypotension may be observed.
- ***Amantadine:*** Increased risk of adverse effects
- ***Aminoglycoside antibiotics:*** diuretic-induced volume depletion can potentiate aminoglycoside nephrotoxicity.
- ***Anticholinergic agents (e.g., atropine, biperidine):*** May increase availability of thiazide diuretics by decreasing gastrointestinal motility and stomach emptying rate.
- ***Antidiabetic drugs (oral agents and insulin):*** Dosage adjustment of the antidiabetic drug may be necessary.
- ***Cholestyramine and colestipol resins:*** HCTZ absorption is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind the HCTZ and reduce its absorption from the gastrointestinal tract by up to 85% and 43%, respectively.
- ***Corticosteroids, ACTH:*** Intensified electrolyte depletion, particularly hypokalemia.
- ***Cytotoxic agents:*** Decreased renal excretion; increased myelosuppressive effects.
- ***Pressor amines (e.g., adrenaline):*** Possible decreased response to pressor amines but not sufficient to prevent their use.
- ***Skeletal muscle relaxants, nondepolarizing (e.g., tubocurarine):*** Possible increased responsiveness to the muscle relaxant.
- ***Lithium:*** Volume depletion increases lithium absorption and may cause lithium toxicity, unless levels are closely monitored and dosage reduced accordingly. Conversely, sudden stopping of diuretic treatment may result in a sub-therapeutic level of circulating lithium.
- ***Nonsteroidal anti-inflammatory drugs (NSAIDs) including COX-2 Inhibitors:*** The administration of NSAIDs including selective COX-2 inhibitors can reduce the diuretic, natriuretic and antihypertensive effects of diuretics in some patients.
- ***Other antihypertensive drugs:*** Additive effect

STATEMENT ON USAGE FOR HIGH RISK GROUPS

PREGNANCY AND LACTATION

Pregnancy

Pregnancy Category C. Amlodipine has been shown to be fetotoxic in laboratory animals. There are no adequate and well-controlled studies in pregnant women.
Thiazides must be avoided during the first trimester of pregnancy. Thiazides cross the placental barrier and appear in cord blood.
Amlodipine + HCTZ should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Lactation

Thiazides appear in human breast milk. It is not known whether amlodipine is excreted in breast milk. Clinicians should consider risk/benefit ratio for breastfeeding women.

INFANTS AND CHILDREN

Safety and effectiveness in children have not been established.

GERIATRICS

Amlodipine besilate:

Observe caution in amlodipine dose selection for an elderly. Elderly patients are more likely to experience a delayed clearance of amlodipine and can be at greater risk for toxicity.

Hydrochlorothiazide:

Thiazide diuretics are more likely to cause hypovolemia, leading to orthostatic hypotension, and reduced glomerular filtration rate can occur. Elderly patients are also more prone to diuretic-induced hypokalemia due to poor dietary intake of potassium.

ADVERSE EFFECTS/UNDESIRABLE EFFECTS

Amlodipine besilate:

Body as a Whole: Asthenia, malaise, pain, fatigue
Nervous System: Hypertonia, hypoesthesia, paresthesia, peripheral neuropathy, tremor, insomnia, mood changes, somnolence, dizziness, headache, vertigo, nervousness, depression, abnormal dreams, anxiety, depersonalization
Cardiovascular: Hypotension, syncope, vasculitis, palpitations, myocardial infarction, arrhythmia (including ventricular tachycardia and atrial fibrillation), tachycardia, flushing, edema, chest pain, peripheral ischemia, postural dizziness, postural hypotension
Gastrointestinal: Dry mouth, thirst, altered bowel habits, dyspepsia, gastritis, gingival hyperplasia, pancreatitis, nausea, vomiting, abdominal pain, constipation, dysphagia, diarrhea, flatulence
Endocrine/Metabolic: Gynecomastia, hyperglycemia, impotence, weight increase/decrease, anorexia
Hematological: Purpura, thrombocytopenia, leukopenia
Skin and Appendages: Increased sweating, alopecia, skin discoloration, urticaria, allergic reactions including pruritus, rash, angioedema, and erythema multiforme, purpura
Urogenital/Reproductive: Increased urinary frequency, micturition disorder, nocturia
Hepatic: Hepatitis, jaundice, hepatic enzyme elevations
Musculoskeletal: Arthralgia, arthrosis, muscle cramps, myalgia, back pain
Respiratory: Coughing, dyspnea, rhinitis, epistaxis
Special senses: Taste perversion, tinnitus, visual disturbances, abnormal vision, conjunctivitis, diplopia, eye pain

HYDROCHLOROTHIAZIDE

Body as a Whole: Fever, fatigue, weakness
Nervous System: Insomnia, cephalalgia, dizziness, restlessness, vertigo, paresthesia, headache
Cardiovascular: Hypotension including orthostatic hypotension (may be aggravated by alcohol, barbiturates, narcotics, antihypertensive drugs), transient cerebral ischemic attacks
Gastrointestinal: Sialadenitis, spasms, stomach irritation, nausea, vomiting, diarrhea, constipation, pancreatitis, cramping, gastric irritation
Endocrine/Metabolic: Anorexia, hyperglycemia, hyperuricemia, hypokalemia, hyponatremia, hypochloremic alkalosis, hypophosphatemia, hypomagnesemia, hypercalcemia, impairment of glucose tolerance, glycosuria, increases in total cholesterol, low density lipoprotein cholesterol (LDL-c), very low density lipoprotein cholesterol (VLDL-c) and triglycerides, impotence
Hematologic: Agranulocytosis, aplastic anemia, hemolytic anemia, leukopenia, thrombocytopenia
Skin and Appendages: Rash, erythema multiforme including Stevens-Johnson syndrome, exfoliative dermatitis including toxic epidermal necrolysis, alopecia, anaphylactic reaction, necrotizing angiitis (vasculitis, cutaneous vasculitis), purpura, urticaria, photosensitivity, polyarteritis nodosa
Urogenital/Reproductive: Glycosuria, interstitial nephritis, renal dysfunction, renal failure, renal impairment
Hepatic: Icterus (intrahepatic cholestatic jaundice)
Musculoskeletal: Muscle cramps, muscle spasm
Respiratory: Respiratory distress including pneumonitis and pulmonary edema
Special senses: Transient blurred vision, xanthopsia

OVERDOSAGE & MANAGEMENT

Amlodipine

Overdosage might be expected to cause excessive peripheral vasodilation with marked hypotension and possibly a reflex tachycardia.
If massive overdose should occur, active cardiac and respiratory monitoring should be given. Frequent blood pressure measurements are necessary. Cardiovascular support including elevation of the extremities and the judicious administration of fluids should be initiated should hypotension occur. 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 to reverse the effects of calcium entry blockade. Hemodialysis is not likely to be of benefit since amlodipine is highly protein bound.

Hydrochlorothiazide

The most common signs and symptoms of HCTZ overdose include electrolyte imbalance (hypokalemia, hypochloremia, hyponatremia) and dehydration resulting from excessive diuresis. Other features of overdose are lethargy, nausea and weakness. Lethargy may progress to coma within a few hours with minimal depression of respiratory and cardiovascular function without evidence of dehydration or serum electrolyte changes. Gastrointestinal irritation and hypermotility may occur, and temporary elevation of blood urea nitrogen has been reported.
In the treatment of thiazide overdosage, gastric contents may be evacuated taking caution to avoid aspiration, particularly in unconscious patients. If the patient is conscious, induction of vomiting with ipecac syrup is effective in removing the drug from the stomach. Do not administer cathartics since they tend to promote loss of fluid and electrolytes. Treatment is generally supportive. Monitor serum electrolyte and renal function. Replacement of fluid and electrolytes may be indicated. Measures may be required to maintain respiratory, cardiovascular and renal function. Gastrointestinal irritation is usually of short duration but may be treated symptomatically.
The degree to which HCTZ is removed by hemodialysis has not been established.

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) UNILAB-1 for Metro Manila or toll free (+1-800) -10-UNILAB-1 for provinces, or email productsafety@unilab.com.ph. By reporting undesirable effects, you can help provide more information on the safety of this medicine.

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

AVAILABILITY

Amlodipine besilate + Hydrochlorothiazide (Amvasc® Plus) 5mg/12.5mg Tablet, in aluminum foil strip x 10's (Box of 30's) (DR-XY38045)
Amlodipine besilate + Hydrochlorothiazide (Amvasc® Plus) 10mg/12.5mg Tablet, in aluminum foil strip x 10's (Box of 30's) (DR-XY38044)

Manufactured by Amherst Laboratories, Inc.
UNILAB Pharma Campus, Barangay Mamplasan
Biñan, Laguna, Philippines
for **UNILAB, Inc.**
No. 66 United Street, Mandaluyong City
Metro Manila Philippines

Trusted Quality Healthcare

DATES OF FIRST AUTHORIZATION

Amlodipine besilate + Hydrochlorothiazide (Amvasc® Plus) 5mg/12.5mg Tablet: June 2010
Amlodipine besilate + Hydrochlorothiazide (Amvasc® Plus) 10mg/12.5mg Tablet: June 2010

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