AMLODIPINE AND BENAZEPRIL b (Systemic)

Indications:

Hypertension (treatment)¾The combination of amlodipine and benazepril is indicated for the treatment of hypertension [1].

It is not indicated as initial treatment for hypertension [1].

Mechanism of action/Effect:

Amlodipine is a dihydropyridine calcium channel blocking agent. [3, 4, 6] Like the other dihydropyridine agents, amlodipine selectively inhibits calcium influx across cell membranes in cardiac and vascular smooth muscle, with a greater effect on vascular smooth muscle. [6] Amlodipine is a peripheral arteriolar vasodilator; thus it reduces afterload. [4, 5]

Benazepril is a nonsulfhydryl angiotensin-converting enzyme (ACE) inhibitor and a prodrug for benazeprilat, the active metabolite. [1] Both benazepril and benazeprilat inhibit ACE. [1] ACE catalyzes the conversion of angiotensin I to the vasoconstrictor angiotensin II. [1] Angiotensin II normally stimulates secretion of aldosterone and inhibits the release of renin through a negative feedback mechanism. [1] When ACE activity is inhibited, angiotensin II formation is decreased and the interruption of the negative feedback mechanism results in increased plasma renin concentrations. [1] The reduction of angiotensin II formation also decreases aldosterone secretion and vasoconstriction. [1] The decrease in aldosterone secretion causes a small increase in serum potassium concentrations. [1] Suppression of the renin-angiotensin-aldosterone system is thought to be the primary mechanism through which ACE inhibitors lower blood pressure. [1]

Other actions/effects:

ACE is also known as kininase, an enzyme that degrades bradykinin. [1, 2] Benazepril may increase concentrations of bradykinin, a potent vasodepressor peptide, but its role in the therapeutic effects of this drug combination has not been determined. [1]

Amlodipine exhibits negative inotropic effects in vivo , [6] but appears to have no significant effect on the sinoatrial (SA) or atrioventricular (AV) node in humans. [4]

Absorption:

Amlodipine¾64 to 90% absorbed. [1] Slowly and almost completely absorbed from the gastrointestinal tract; [3, 4, 7] absorption not affected by food. [6, 8]

Benazepril¾Approximately 37% absorbed. [1]

Distribution:

Volume of distribution (Vol D)¾ Amlodipine: 21 L per kg (L/kg). [1]

Benazeprilat: 0.7 L/kg, concentration-independent. [1]

Protein binding:

Amlodipine¾Very high (Approximately 93%). 1, 6

Benazeprilat¾Very high (95.3%). 2

Biotransformation:

Amlodipine¾Undergoes minimal presystemic metabolism. 4, 7 Amlodipine undergoes slow but extensive hepatic metabolism, producing metabolites lacking significant pharmacological activity. 4, 7, 9

Benazepril¾Almost completely converted, primarily in the liver, to its active metabolite, benazeprilat. 1

Half-life:

Elimination¾ Amlodipine: Mean, 35 hours in healthy volunteers; 4, 7, 11, 9, 10, 12, 13 may be prolonged to a mean of 48 hours in hypertensive patients, 4, 7 65 hours in the elderly, 4, 7, 14 and 60 hours in patients with hepatic function impairment. 4, 7, 16 Not significantly affected by renal function impairment. 6, 15

Benazeprilat: 10 to 11 hours. 1

Time to peak concentration:

Amlodipine¾6 to 12 hours. 1, 7, 9, 11

Benazepril¾0.5 to 2 hours. 1

Benazeprilat¾1.5 to 4 hours. 1

Duration of action:

Amlodipine¾24 hours. 7

Benazeprilat¾24 hours. 2

Elimination:

Amlodipine¾ Biliary/fecal¾20 to 25%. 4, 7, 12

Renal: Approximately 70% (10% as amlodipine and 60% as metabolites). 1, 6

Benazepril¾ Primarily renal, but also biliary. 1

In dialysis¾ Amlodipine: Not reported to be removable by hemodialysis. 1

Benazeprilat: Slightly removable by hemodialysis. 1

Precautions to Consider

Cross-sensitivity and/or related problems

Patients hypersensitive to other angiotensin-converting enzyme (ACE) inhibitors also may be hypersensitive to benazepril. 1

Carcinogenicity

No evidence of carcinogenicity was found in rats or mice given amlodipine for 2 years at dietary doses of 0.5, 1.25, and 2.5 mg per kg of body weight (mg/kg) per day. 1 For mice, the highest dose is approximately the maximum recommended human daily dose (MRHDD) on a mg per square meter of body surface area (mg/m 2) basis and is close to the maximum tolerated dose. 1 For rats, this dose is approximately twice the MRHDD 1 , on a mg/m 2 basis.
No evidence of carcinogenicity was found in rats or mice given benazepril for 104 weeks at doses of up to 150 mg/kg per day. This represents more than 100 times the MRHDD, based on body weight. 1 Based on body surface area, this represents 18 and 9 times the MRHDD for rats and mice, respectively. 1

Mutagenicity

Mutagenicity was not detected for amlodipine in studies at either the gene or chromosome level. 1

Mutagenicity was not detected for benazepril in the Ames test in bacteria, in an in vitro test for forward mutations in cultured mammalian cells, or in a nucleus anomaly test. 1

Pregnancy/Reproduction

Fertility¾No impairment of fertility was found in male or female rats treated with amlodipine 64 days and 14 days prior to mating, respectively, at doses of up to 10 mg/kg per day (eight times the MRHDD of 10 mg, on a mg/m 2 basis, assuming a 50-kg person). 1

Reproductive performance of male and female rats was not affected when given benazepril at doses of 50 to 500 mg/kg per day. 1 This represents 38 to 375 times the MRHDD on a body weight basis and 6 to 61 times the MRHDD on a body surface area basis. 1

No impairment of fertility was found when amlodipine and benazepril combination was given to male and female rats. 1 Amlodipine was administered at daily doses of up to 7.5 mg/kg and benazepril at daily doses of up to 15 mg/kg per day prior to mating and throughout gestation. 1

Pregnancy¾ACE inhibitors can cause fetal and neonatal morbidity and mortality when administered to pregnant women during the second and third trimesters. 1 Amlodipine and benazepril combination should be discontinued as soon as possible when pregnancy is detected unless no alternative therapy can be used. 1 In the latter instance, serial ultrasound examinations should be performed to assess the intra-amniotic environment. 1 If oligohydramnios is observed, amlodipine and benazepril combination should be discontinued unless it is considered lifesaving for the mother. 1 Perinatal diagnostic tests, such as contraction-stress testing (CST), a nonstress test (NST), or biophysical profiling (BPP), also may

be appropriate during the applicable week of pregnancy. 1 Oligohydramnios may not be apparent until after the fetus has sustained irreversible damage. 1

Fetal exposure to ACE inhibitors during the second and third trimesters can cause hypotension, reversible or irreversible renal failure, anuria, neonatal skull hypoplasia, and death in the fetus or neonate. 1 Maternal oligohydramnios, which may result from decreased fetal renal function, has been reported and is associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. 1 Other adverse effects that have been reported are prematurity, intrauterine growth retardation, and patent ductus arteriosus, although how these effects are related to exposure to ACE inhibitors is not clear. 1 ACE inhibitor exposure, when limited to the first trimester, does not appear to be associated with these adverse effects. 1

Infants exposed in utero to ACE inhibitors should be observed closely for hypotension, oliguria, and hyperkalemia. 1 Oliguria should be treated with support of blood pressure and renal perfusion. 1 Dialysis or exchange transfusion may be necessary to reverse hypotension and/or substitute for disordered renal function. 1

Teratogenic effects were not observed in rabbits given daily combination doses of benazepril 1.5 mg/kg and amlodipine 0.75 mg/kg or in rats given daily combination doses of benazepril 50 mg/kg and amlodipine 25 mg/kg. 1 These doses represent 0.97 and 24 times the maximum recommended human dose of the combination, respectively, on a mg/m 2 of body surface area basis, assuming a 50-kg woman. 1

FDA Pregnancy Category C (first trimester). 1

FDA Pregnancy Category D (second and third trimesters). 1

Labor¾Dystocia was observed in rats given daily combination doses ranging from amlodipine 2.5 mg/kg and benazepril 5 mg/kg to amlodipine 25 mg/kg and benazepril 50 mg/kg. 1 The 2.5 mg/kg per day dose of amlodipine is 3.6 times the amlodipine dose delivered, on a mg/m 2 basis, when the maximum recommended human dose of the combination is given to a 50-kg woman. 1 The 5 mg/kg per day dose of benazepril represents approximately two times the benazepril dose delivered, on a mg/m 2 basis, when the maximum recommended dose of the combination is given to a 50-kg woman. 1

Dental

Gingival hyperplasia is a rare side effect that has been reported with amlodipine. 18 It also has been reported with other calcium channel blocking agents, such as diltiazem, felodipine, verapamil, and, most commonly, nifedipine. 17 It usually starts as gingivitis or gum inflammation in the first 1 to 9 months of treatment. Resolution of the hyperplasia and improvement of the clinical symptoms usually occur one to four weeks after discontinuation of therapy. 17 A strictly enforced program of professional teeth cleaning combined with plaque control by the patient will minimize growth rate and severity of gingival enlargement. Periodontal surgery may be indicated in some cases, and should be followed by careful plaque control to inhibit recurrence of gum enlargement.

Side/Adverse Effects

The following side/adverse effects have been selected on the basis of their potential clinical significance (possible signs and symptoms in parentheses where appropriate)¾not necessarily inclusive:
Those indicating need for medical attention

Incidence less frequent

Edema, dependent 1 swelling of ankles, feet, and lower legs)¾the incidence of amlodipine-associated edema is reduced when amlodipine is given in combination with benazepril 1; hyperkalemia 1 confusion); irregular heartbeat); nervousness); numbness or tingling in hands, feet, or lips); shortness of breath or difficulty breathing); weakness or heaviness of legs)¾during clinical trials, hyperkalemia occurred in approximately 1.5% of patients 1; hypotension 1 dizziness, lightheadedness, or fainting)
Incidence rare

Anemia, hemolytic 1 bleeding gums); fatigue); nosebleeds); pale skin color); angioedema 1 sudden trouble in swallowing or breathing); swelling of face, mouth, hands, or feet); hoarseness); hepatotoxicity 1 yellow eyes or skin); neutropenia or agranulocytosis 1 chills); fever); sore throat)¾occurs rarely in uncomplicated hypertension; occurs more frequently in patients with renal function impairment, especially if accompanied by a collagen-vascular disease 1; pancreatitis 1 abdominal pain and distention); fever); nausea); vomiting); pemphigus 1 blisters in the mouth followed by skin blisters on the trunk, scalp, or other areas); Stevens-Johnson syndrome 1 sudden onset of multiple skin lesions on the arms, feet, hands, legs, palms, mouth, and/or lips); thrombocytopenia 1 unusual bleeding or bruising)

Note: Angioedema is associated with ACE inhibitor therapy and may involve the face, extremities, lips, tongue, glottis, and larynx 1.

Angioedema associated with laryngeal edema, resulting in airway obstruction, can be fatal 1.

During clinical trials, angioedema occurred in 0.5% of patients taking benazepril alone 1.

ACE inhibitor-associated angioedema occurs at a higher rate in black patients than in nonblack patients 1.

ACE inhibitor-associated hepatotoxicity occurs by a mechanism that is not understood, but is manifest as a syndrome of cholestatic jaundice, fulminant hepatic necrosis, and possibly death 1.

Amlodipine and benazepril combination therapy should be discontinued in patients who develop jaundice or marked elevations of hepatic enzymes 1.

Patients should receive appropriate medical follow-up 1.

Those indicating need for medical attention only if they continue or are bothersome

Incidence less frequent

Cough, dry and persistent 1; dizziness 1; flushing 1; palpitations 1 (heartbeat sensations); somnolence 1 (sleepiness)