Angiotensin Modulator Combinations
Therapeutic Class Review (TCR)

December 2, 2021

The materials contained herein represent the opinions of the collective authors and editors and should not be construed to be the official representation of any professional organization or group, any state Pharmacy and Therapeutics committee, any state Medicaid Agency, or any other clinical committee. This material is not intended to be relied upon as medical advice for specific medical cases and nothing contained herein should be relied upon by any patient, medical professional or layperson seeking information about a specific course of treatment for a specific medical condition. All readers of this material are responsible for independently obtaining medical advice and guidance from their own physician and/or other medical professional in regard to the best course of treatment for their specific medical condition. This publication, inclusive of all forms contained herein, is intended to be educational in nature and is intended to be used for informational purposes only. Send comments and suggestions to PSTCREditor@magellanhealth.com.

FDA-APPROVED INDICATIONS

Drug	Manufacturer	Indication(s)
amlodipine/benazepril (Lotrel®)[1]	generic, Novartis	Hypertension (not as initial therapy)
amlodipine/olmesartan (Azor®)[2]	generic, Daiichi Sankyo	Treatment of hypertension either alone or in combination with other agents Initial therapy in patients likely to need multiple antihypertensive agents to achieve their blood pressure goals
amlodipine/olmesartan/HCTZ (Tribenzor®)[3]	generic, Daiichi Sankyo	Hypertension (not as initial therapy)
amlodipine/perindopril (Prestalia®)[4]	Adhera	Treatment of hypertension for patients not adequately controlled on monotherapy Initial treatment of hypertension in patients who will likely require multiple medications for blood pressure control
amlodipine/telmisartan (Twynsta®)[5]	generic, Boehringer Ingelheim	Treatment of hypertension alone or in combination with other agents Initial treatment of hypertension in patients who will likely require multiple medications for blood pressure control
amlodipine/valsartan (Exforge®)[6]	generic, Novartis	Initial treatment of hypertension in patients who will likely require multiple medications for blood pressure control Treatment of hypertension for patients not adequately controlled on monotherapy
amlodipine/valsartan/HCTZ (Exforge HCT®)[7]	generic, Novartis	Hypertension (not initial therapy)
verapamil sustained-release (SR)/trandolapril[8]	Glenmark	Hypertension (not as initial therapy)

HCTZ = hydrochlorothiazide

OVERVIEW

Approximately half a million adults in the United States (US) have hypertension as a primary or contributing cause of death.[9] Prevalence of high blood pressure is higher in the African American population; approximately 56% of African American men and women compared to about 48% of white men and women have hypertension. It is estimated that hypertension is controlled in only about 24% of patients with the condition. Hypertension is an independent risk factor for cardiovascular disease, stroke, and renal dysfunction and can lead to heart failure (HF) and stroke if uncontrolled for a prolonged period.[10]

The US Preventive Services Task Force (USPSTF) recommends annual hypertension screening for adults aged ≥ 40 years and patients who are at increased risk for high blood pressure (e.g., persons with high-normal blood pressure, overweight or obese, African Americans).[11] Adults aged 18 to 39 years with normal blood pressure (< 130/85 mm Hg) who do not have other risk factors should be rescreened every 3 to 5 years. USPSTF recommends office blood pressure measurement (OBPM) along with obtaining blood pressure measurements outside of the clinical setting for diagnostic confirmation before starting treatment.

The 2014 Eighth Report from the National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-8) in general recommends to start antihypertensive therapy in patients at least 60 years of age when systolic blood pressure (SBP) is 150 mm Hg or greater or diastolic blood pressure (DBP) is 90 mm Hg or greater, with a goal of SBP < 150 mm Hg and DBP < 90 mm Hg.[12] For patients younger than 60 years and adults with chronic kidney disease (CKD), therapy should be initiated when SBP ≥ 140 mm Hg and DBP ≥ 90 mm Hg and target blood pressure is less than 140/90 mm Hg. In the non-African American population, initial treatment should include a thiazide-type diuretic, calcium channel blocker (CCB), angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB). For African Americans, initial treatment should include a thiazide-type diuretic or CCB. In patients with CKD treatment should include an ACE inhibitor or ARB to improve kidney function, regardless of race or diabetes status. If blood pressure goal is not reached within 1 month of starting treatment, the dose should be increased or a second a drug from another class should be added; a third drug can be added if needed. Most hypertensive patients require at least 2 medications to achieve adequate blood pressure (BP) reduction as seen in a large clinical trial.[13]

The American College of Physicians (ACP) and American Academy of Family Physicians (AAFP) published evidence-based recommendations on the benefits and harms of higher (< 150 mm Hg) versus lower (< 140 mm Hg) SBP targets in the treatment of hypertensive adults ages 60 years and older.[14] The ACP and AAFP recommend initiating antihypertensive therapy in adults 60 years and older with SBP ≥ 150 mm Hg; target SBP is less than 150 mm Hg to reduce the risk of mortality, stroke, and cardiac events (strong recommendation, high-quality evidence). A stricter goal of SBP < 140 mm Hg may be considered in older adults with a history of stroke or transient ischemic attack and those with a high cardiovascular disease (CVD) risk.

The American College of Cardiology (ACC) and American Heart Association (AHA), along with other relevant medical organizations, issued a 2017 guideline on the prevention, detection, evaluation, and management of high blood pressure.[15] The guideline revised the classification system for blood pressure. Drug therapy is based on a combination of average BP, atherosclerotic CVD risk, and comorbid conditions. For high-risk (preexisting CVD or estimated 10-year risk of ≥ 10%) adults with stage 1 hypertension, defined as average SBP of 130 to 139 mm Hg or DBP 80 to 89 mm Hg, treatment should be initiated in patients with a BP of ≥ 130/80 mm Hg (class I recommendation). For lower-risk adults, ACC/AHA specifies the threshold BP for drug treatment at ≥ 140/90 mm Hg (class I recommendation). Regardless of risk, the goal BP after initiating treatment is < 130/80 mm Hg. First-line therapy recommendations include thiazide diuretics, CCBs, and ACE inhibitors or ARBs (class I recommendation). Patients in stage 2 hypertension (SBP ≥ 140 mm Hg or DBP ≥ 90 mm Hg) should be initiated with 2 first-line treatment agents with differing mechanisms of action (class I recommendation). In 2021, the American Heart Association (AHA) published a Scientific Statement that is complementary to the 2017 ACC/AHA guidelines reinforcing the guidelines recommended for patients with a low 10-year risk (CVD < 10%).[16]

In 2019, the ACC and AHA published updated guidelines on the primary prevention of cardiovascular disease.[17] The guidelines recommend that nonpharmacological interventions are the preferred therapy for adults with elevated BP and an appropriate first-line therapy for adults with stage 1 hypertension who have an estimated 10-year ASCVD risk of < 10%. The guidelines reinforce the 2017 ACC/AHA guidelines on management for blood pressure and state that BP-lowering medications provide benefit on ASCVD prevention in adults with moderate to high ASCVD risk and SBP ≥ 130 mm Hg or DBP ≥ 80

mm Hg via significant reduction in stroke, heart failure, coronary events, and death. Furthermore, achieving an additional 10-mm Hg reduction in SBP reduces CVD risk.

Additionally, in 2019, the AHA/ACC issued a report regarding the quality measures for adults with high blood pressure, revising earlier guidance from 2011.[18] The committee developed a comprehensive measure set for the diagnosis and treatment of high blood pressure. These recommendations do not change overall clinical recommendations, but they offer management targets for providers.

In 2018, the AHA updated the Scientific Statement on resistant hypertension (RH). The AHA defines RH as above-goal elevated blood pressure (BP) despite concurrent use of 3 antihypertensive drug classes at maximally tolerated doses or BP that requires ≥ 4 medications to achieve a target level.[19] Hypertension is typically treated with a diuretic, a long-acting calcium channel blocker, and a renin-angiotensin system blocker (angiotensin-converting enzyme [ACE] inhibitor or angiotensin receptor blocker [ARB]). Similar to the 2017 ACC/AHA, the BP target of ≤ 130/80 mm Hg in patients on antihypertensive therapy. Diagnosis of RH should be made based on a 24-hour ambulatory BP measured after medication adherence has been confirmed. RH assessment should consider lifestyle, drug-drug interactions, secondary hypertension, and presence of end organ damage. Recommended treatment for confirmed RH includes optimization of lifestyle interventions, use of a long-acting thiazide-like diuretic (e.g., chlorthalidone, indapamide), and addition of a mineralocorticoid receptor antagonist (e.g., spironolactone, eplerenone). If BP remains above target levels, addition of agents with different mechanisms, and possibly referral to a hypertension specialist, are advised.

For patients with diabetes and hypertension, the American Diabetes Association (ADA) recommends a BP treatment goal of < 130/80 mm Hg in patients with high CVD risk (existing atherosclerotic CVD [ASCVD] or 10-year ASCVD risk > 15%) and BP goal of < 140/90 mm Hg for those at lower CVD risk (10-year ASCVD < 15%).[20]

In 2020, the Kidney Disease: Improving Global Outcomes (KDIGO) organization published its first guideline on managing diabetes in patients with chronic kidney disease (CKD).[21] They recommend that patients with diabetes, hypertension, and albuminuria should start treatment with an ACE inhibitor or ARB along with regular glycemic control, targeting A1c in their specific target range. In the 2021 KDIGO guidelines update, they recommend the target systolic BP be < 120 mm Hg in most patients with CKD, with the exception of kidney transplant recipients and children.[22]

In 2018, the AHA issued a Scientific Statement on the intersection of CVD and breast cancer.[23] CVD and breast cancer have several overlapping risk factors, such as obesity and smoking. Additionally, current breast cancer treatments can have a negative impact on cardiovascular health (e.g., left ventricular dysfunction, accelerated CVD), and for women with pre-existing CVD, this might influence cancer treatment decisions by both the patient and the provider. The Scientific Statement details select risk factors that may pose a greater risk for cardiotoxicity.

In 2019, the AHA issued a Scientific Statement regarding the accurate measurement of blood pressure (BP).[24] Ambulatory BP monitoring is considered the standard for out-of-office BP assessment. Automated oscillometric devices have been validated to provide accurate BP measurements while reducing human errors, even without an observer being present.

PHARMACOLOGY[25,26,27,28,29,30,31,32,33]

These agents are a fixed-dose combination of 2 or 3 of the following: an angiotensin II receptor blocker (ARB) or an angiotensin-converting enzyme (ACE) inhibitor in combination with a calcium channel blocker (CCB) or a beta blocker, with or without the addition of a thiazide diuretic.

ACE inhibitors included in this class of combination products include benazepril, perindopril, and trandolapril, components of Lotrel, Prestalia, and verapamil sustained-release (SR)/trandolapril, respectively.

ACE inhibitors prevent the conversion of angiotensin I to angiotensin II, a potent vasoconstrictor, by competing with angiotensin I for the active site of ACE. The reduction of angiotensin II formation decreases vasoconstriction, decreases aldosterone secretion, and increases plasma renin. This causes a reduction in blood pressure and total peripheral resistance, and decreased sodium and water retention. There is also a possible local action within the vascular wall that is responsible for blood pressure reduction.

Azor, Twynsta, and Exforge contain olmesartan, telmisartan, and valsartan, respectively, which are angiotensin II receptor blockers. Angiotensin II causes vasoconstriction, release of aldosterone and antidiuretic hormone, sympathetic activation, and constriction of the efferent arterioles of the glomerulus in the kidneys. ARBs block the vasoconstrictive and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor found in many tissues, such as vascular smooth muscle and the adrenal gland. Non-ACE pathways also produce angiotensin II. ARBs do not inhibit ACE (kinase II, the enzyme that converts angiotensin I to angiotensin II and degrades bradykinin), nor do they bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

Calcium channel blockers inhibit calcium ions from moving across the cell membrane. The limitation of calcium entering into the cells causes a decrease in mechanical contraction of myocardial and smooth muscle, thereby causing dilation of systemic arteries and a decrease in total peripheral resistance, systemic blood pressure, and the afterload of the heart. The dihydropyridine CCB amlodipine (a component of Lotrel, Azor, Tribenzor, Prestalia, Twynsta, Exforge, and Exforge HCT) is a potent vasodilator and can increase or have a neutral effect on vascular permeability. The nondihydropyridine CCB verapamil is a potent vasodilator, but verapamil has a greater depressive effect on cardiac conduction and contractility.

Hydrochlorothiazide (HCTZ; a component of Tribenzor and Exforge HCT) is a thiazide diuretic that exhibits its pharmacological effects by blocking the reabsorption of sodium and chloride leading to diuresis and a reduction in intravascular volume. Concurrent administration of an angiotensin II receptor antagonist, such as valsartan, and a thiazide diuretic may help to decrease potassium loss that occurs with thiazide diuretic therapy.

Blood pressure is lowered through the antihypertensive mechanisms of all components of the combinations.

PHARMACOKINETICS[34,35,36,37,38,39,40,41,42]

There are no pharmacokinetic profile changes with combination products versus each single agent, except with verapamil SR 240 mg/trandolapril 4 mg, in which an increase in area under the curve (AUC) and maximum serum concentration (Cmax) are seen with verapamil.

Brand Name	Generic Name	Bioavailability (%)	Half-Life (hr)	Metabolites	Excretion (%)
Lotrel	amlodipine	64-90	~48	extensively metabolized	Urine: 70
	benazepril	> 37	10-11	benazeprilat (~100%)	Primarily urine
Azor	amlodipine	64-90	30-50	extensively metabolized	Urine: 70
	olmesartan	26	13	none significant	Feces: 50-65 Urine: 35-50
Tribenzor	amlodipine	64-90	30-50	extensively metabolized	Urine: 55
	olmesartan	26	13	none significant	Feces: 50-65 Urine: 35-50
	hydrochlorothiazide	--	5.6-14.8	not metabolized	Urine: 61
Prestalia	amlodipine	64-90	30-50	extensively metabolized	Urine: 70
	perindopril	75 (as perindopril)	1.3	perindoprilat	Urine: 75 Feces: 25
Twynsta	amlodipine	64-90	30-50	extensively metabolized	Urine: 70
	telmisartan	42-58	24	metabolized to glucuronide conjugate	Feces: > 97
Exforge	amlodipine	64-90	30-50	extensively metabolized	Urine: 70
	valsartan	25	6	20% of dose converted to metabolites	Urine: 13 Feces: 83
Exforge HCT	amlodipine	64-90	30-50	extensively metabolized	Urine: 70
	hydrochlorothiazide	--	5.8-18.9	not metabolized	Urine: 61
	valsartan	10-35	6	20% of dose converted to metabolites	Urine: 13 Feces: 83
verapamil sustained-release (SR)/trandolapril	trandolapril	10 (as trandolapril)	10	trandolaprilat	Urine: 33 Feces: 66
	verapamil SR	20-35	6-11	12 metabolites; norverapamil is 20% as potent as parent	Urine: 70 Feces: 16

CONTRAINDICATIONS/WARNINGS[43,44,45,46,47,48,49,50]

Hypersensitivity to any of these products is considered a contraindication.

All product labeling for agents in this review contain boxed warnings regarding the use of drugs that act directly on the renin-angiotensin-aldosterone system during pregnancy can cause fetal and neonatal morbidity and death and, when pregnancy is detected, should be discontinued as soon as possible.

Angioedema of the head and neck can occur with any angiotensin modulating agent. If angioedema involves the tongue or airway, respiratory distress may occur and could result in death without prompt treatment. Combination agents containing an ACE inhibitor should not be used in patients who have experienced angioedema related to previous ACE inhibitor therapy. Patients taking concomitant mammalian target of rapamycin (mTOR) inhibitors (e.g., everolimus, sirolimus, temsirolimus) or a neprilysin inhibitor may be at an increased risk of angioedema.

Agents in this class are contraindicated in combination with a neprilysin inhibitor (e.g., sacubitril) and they should not be administered within 36 hours of switching to or from sacubitril/valsartan (Entresto®).

Agents with a hydrochlorothiazide component are contraindicated in patients with anuria.

Renal function should be monitored periodically. Changes in renal function, including acute renal failure, can be caused by drugs that affect the renin-angiotensin system. In patients who develop a clinically significant decrease in renal function, withholding or discontinuing therapy should be considered.

Dual blockade of the renin-angiotensin-aldosterone system is associated with increased risk of hypotension, syncope, hyperkalemia, and changes in renal function (including acute renal failure). Closely monitor blood pressure, renal function, and electrolytes in patients on ACE inhibitors and ARBs.

Volume- or salt-depleted patients are more likely to have hypotension.

Olmesartan, one of the components of Azor and Tribenzor, can cause hyperkalemia as it is an inhibitor of the renin-angiotensin system. Therefore, serum electrolytes must be monitored regularly.

In both the Randomized Olmesartan and Diabetes Microalbuminuria Prevention (ROADMAP) and Olmesartan Reducing Incidence of End Stage Renal Disease in Diabetic Nephropathy Trial (ORIENT) trials, patients with type 2 diabetes were given either olmesartan or placebo to determine if treatment with olmesartan would slow the progression of kidney disease. An unexpected finding observed in both trials was a greater number of deaths from a cardiovascular cause (MI, sudden death, or stroke) in the olmesartan-treated patients compared to placebo. The Food and Drug Administration (FDA) has completed its safety review in which patients with type 2 diabetes were taking olmesartan (Benicar) and found no clear evidence of a higher rate of cardiovascular risk as compared to placebo.[51] The FDA reminds practitioners that numerous clinical trials with olmesartan, as well as trials with other ARBs, have not suggested an increased risk of cardiovascular-related death. Currently, the FDA still believes that the benefits of olmesartan in patients with hypertension continue to outweigh the potential risks. However, the labeling for amlodipine/olmesartan states that it should not be used in patients with diabetes.

Sprue-like enteropathy has been reported in patients taking olmesartan months to years after starting the drug. Severe chronic diarrhea with substantial weight loss has been reported; if a patient develops these symptoms while on olmesartan, other etiologies must be excluded. Stopping olmesartan therapy in cases where no other etiologies are identified should be considered.

In July 2010, the FDA announced that they were conducting a review of ARBs after a meta-analysis including data from over 60,000 patients suggested that ARBs may be associated with a small increased risk of cancer.[52] In June 2011, the FDA concluded that treatment with an ARB does not increase cancer risk.[53] To draw this conclusion, the FDA conducted a trial-level meta-analysis of 31 clinical trials in

which patients were randomized to treatment with an ARB (n=84,461) or a non-ARB (n=71,355). The meta-analysis evaluated the association between ARBs and the risk of incident (new) cancer, cancer-related death, breast cancer, lung cancer, and prostate cancer. The rate of cancer events in the ARB group was 1.82 per 100 patient-years compared to 1.84 per 100 patient-years in non-ARB comparators. The relative risk of cancer in patients taking ARBs was 0.99 (95% confidence interval [CI], 0.92 to 1.06). The FDA also found no evidence of association between ARBs and cancer-related death (relative risk [RR], 1.04; 95% CI, 0.96 to 1.13), breast cancer (odds ratio [OR], 1.06; 95% CI, 0.9 to 1.23), lung cancer (OR, 1.07; 95% CI, 0.89 to 1.29), or prostate cancer (OR, 1.05; 95% CI, 0.95 to 1.17). In 2011, another meta-analysis assessed the association between antihypertensive drugs and cancer risk.[54] It included 70 randomized controlled trials with 324,168 participants and recorded no difference in the risk of cancer with ARBs. There was an increased risk with the combination of ACE Inhibitors plus ARBs (2.3%; OR, 1.14; 95% CI, 1.02 to 1.28); however, this risk was not apparent in the random-effects model (OR, 1.15; 95% CI, 0.92 to 1.38).

Due to the verapamil component, verapamil SR/trandolapril is contraindicated in patients with severe left ventricular dysfunction (LVD), hypotension (systolic blood pressure [SBP] < 90 mm Hg), cardiogenic shock, sick sinus syndrome (except in patients with a functioning artificial ventricular pacemaker), second or third degree AV block (except in patients with a functioning artificial ventricular pacemaker), atrial flutter or atrial fibrillation, and an accessory bypass tract (e.g., Wolff-Parkinson-White, Lown-Ganong-Levine syndromes).

Amlodipine/valsartan/HCTZ (Exforge HCT) and amlodipine/olmesartan/HCTZ (Tribenzor) are contraindicated in patients with anuria or hypersensitivity to other sulfonamide-derived drugs due to the hydrochlorothiazide component. Thiazide diuretics may also cause exacerbation or activation of systemic lupus erythematosus. The potential exists for electrolyte (e.g., hypercalcemia, hypochloremic alkalosis, hypokalemia, hypomagnesemia, hyponatremia, and hyperuricemia) or fluid imbalances; monitoring is recommended. Hydrochlorothiazide may alter glucose tolerance and raise serum levels of cholesterol and triglycerides.

Worsening angina and acute myocardial infarction may develop after beginning or increasing the dose of amlodipine, especially in patients with severe obstructive coronary artery disease.

Appropriate caution is necessary when using amlodipine in patients suffering from aortic or mitral stenosis, or obstructive hypertrophic cardiomyopathy.

Hydrochlorothiazide can cause an idiosyncratic reaction, resulting in acute transient myopia and acute angle-closure glaucoma. Symptoms, such as acute onset of decreased visual acuity or ocular pain, can occur within hours to weeks of drug initiation. If untreated, acute angle-closure glaucoma can lead to permanent vision loss. Hydrochlorothiazide should be discontinued as rapidly as possible. Prompt medical or surgical treatments may be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulfonamide or penicillin allergy.

In August 2020, the FDA approved label changes for drugs containing HCTZ in order to notify practitioners and patients about the small but increased risk of non-melanoma skin cancer (basal cell skin cancer or squamous cell skin cancer) associated with HCTZ. In addition, patients should be reminded to use skin protection.[55]

DRUG INTERACTIONS[56,57,58,59,60,61,62,63]

ACE inhibitors interact with azathioprine, cyclosporine, lithium, nonsteroidal anti-inflammatory drugs (NSAIDs), potassium sparing diuretics, trimethoprim, and eplerenone (Inspra®). Concurrent use of loop and thiazide diuretics can increase the risk of hypovolemia and increase the risk of nephrotoxicity.

The risk of angioedema may be increased with concurrent use of ACE inhibitors and mTOR inhibitors. Patients taking concomitant neprilysin inhibitors (e.g., sacubitril) may be at an increased risk of angioedema.

Increases in serum lithium concentrations and lithium toxicity have been reported with concurrent use of lithium and ARBs. Serum lithium levels should be monitored with concurrent use. Verapamil can interact with digoxin, lithium, erythromycin, clarithromycin, beta-blockers, carbamazepine, rifampin, phenobarbital, cyclosporine, theophylline, and select antiarrhythmic agents.

In elderly volume-depleted (including those on diuretic therapy) or renally-compromised patients, co-administration of NSAIDs, including selective COX-2 inhibitors, with agents acting on the renin-angiotensin system (ACE inhibitors, ARBs) may result in decreased renal function, including possible acute renal failure. These effects are usually reversible. Monitor renal function periodically in patients receiving ACE inhibitors or ARBs, with NSAID therapy. In addition, the antihypertensive effect of ACE inhibitors and ARBs may be reduced by NSAIDs, including selective COX-2 inhibitors.

Co-administration of multiple doses of amlodipine or verapamil with 80 mg simvastatin may result in a significant increase in exposure to simvastatin. Simvastatin dose should not exceed 20 mg per day in patients on amlodipine. For patients on verapamil, limit the dose of simvastatin to 10 mg daily and the dose of lovastatin to 40 mg. Lower starting and maintenance doses of other CYP3A4 substrates (e.g., atorvastatin) may be required as verapamil may increase the plasma concentration of these drugs.

Coadministration of amlodipine with moderate or strong CYP3A inhibitors can result in increased systemic exposure to amlodipine; additional monitoring and a dose adjustment may be required.

Amlodipine may increase the systemic exposure of cyclosporine or tacrolimus when administered together. Monitoring of trough blood levels of cyclosporine and tacrolimus is recommended, and dosage adjustment may be needed.

Concomitant use of verapamil and ivabradine may increase exposure to ivabradine and lead to exacerbation of bradycardia and conduction disturbances. Co-administration of verapamil and ivabradine must be avoided.

Verapamil is a P-gp blocker and may increase exposure to the direct thrombin inhibitor dabigatran upon concurrent administration. Dose adjustments for dabigatran is not necessary in such cases.

Hydrochlorothiazide may potentiate the orthostatic effects of alcohol, barbiturates, or narcotics; interact with oral antidiabetic drugs and insulin requiring a dose adjustment of the antidiabetic agent; impair the absorption of HCTZ with anionic exchange resins (such as cholestyramine); intensify electrolyte depletion with corticosteroids; reduce lithium clearance; and lead to symptomatic hyponatremia with carbamazepine. NSAIDs can reduce diuretic, natriuretic, and antihypertensive effects of diuretics.

No drug interaction studies have been conducted with amlodipine/valsartan (Exforge) or amlodipine/valsartan/HCTZ (Exforge HCT).

ADVERSE EFFECTS[64,65,66,67,68,69,70,71]

Drug	Cough	Headache	Dizziness	Edema
amlodipine (n=475)	0.4	2.9	2.3	5.1
benazepril (n=554)	1.8	3.8	1.6	0.9
amlodipine/benazepril (Lotrel) (n=760)	3.3	2.2	1.3	2.1
placebo (n=408)	0.2	5.6	1.5	2.2

Drug	Nasopharyngitis	Headache	Fatigue	Peripheral Edema
amlodipine/olmesartan/HCTZ (Tribenzor) (n=574)	3.5	6.4	4.2	7.7
olmesartan/HCTZ (n=580)	3.4	6.6	5.3	1
amlodipine/olmesartan (n=596)	1.8	7	5.7	7
HCTZ/amlodipine (n=552)	2.9	6	6.5	8.3

Drug	Cough	Headache	Dizziness	Peripheral Edema
amlodipine (n=280)	0.7	2.9	1.1	13.2
perindopril (n=278)	2.9	2.9	1.4	0.4
amlodipine/perindopril (Prestalia) (n=279)	3.2	2.5	2.5	7.2

Drug	Back pain	Dizziness	Peripheral Edema	Other Edema
amlodipine/telmisartan (Twynsta) (n=789)	2.2	3	4.8	< 2
placebo (n=46)	0	2.2	0	nr

Drug	Nasopharyngitis	URTI	Dizziness	Peripheral Edema
amlodipine/valsartan (Exforge) (n=1,437)	4.3	2.9	2.1	5.4
placebo (n=337)	1.8	2.1	0.9	3

Drug	Dyspepsia	Headache	Dizziness	Edema
amlodipine/valsartan/HCTZ (Exforge HCT) (n=582)	2.2	5.2	8.2	6.5
valsartan/HCTZ (n=559)	0.9	5.5	7.2	1.4
amlodipine/valsartan (n=566)	1.1	5.3	2.5	11.5
HCTZ/amlodipine (n=561)	0.4	7.1	4.1	11.2

Drug	Cough	Headache	Dizziness	Edema
verapamil SR/trandolapril (n=541)	4.6	8.9	3.1	1.3
placebo (n=206)	2.4	9.7	1.9	2.4

URTI = Upper Respiratory Tract Infection

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative or all inclusive.

The overall incidence of adverse reactions for amlodipine/olmesartan (Azor) was similar to that seen with corresponding doses of the individual components and to placebo. Edema was the most frequently reported adverse effect (≥ 3%) in the amlodipine/olmesartan (Azor) group compared to placebo.

SPECIAL POPULATIONS[72,73,74,75,76,77,78,79]

Pediatrics

Due to the fixed-dose combinations of this class, the Angiotensin Modulators Combinations class does not lend itself for use in pediatric patients. Safety and effectiveness in pediatric patients using the combination products have not been established.

Pregnancy

Use of medications that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Most studies evaluating fetal abnormalities after exposure during the first trimester have not found distinguishable differences compared to other antihypertensive agents. All products carry a boxed warning regarding fetal toxicity. When pregnancy is detected, discontinue medication as soon as possible.

Previously, all products in this review were Pregnancy Category D. In compliance with the Pregnancy and Lactation Labeling Rule (PLLR), the labeling for amlodipine/telmisartan (Twynsta), amlodipine/valsartan (Exforge), amlodipine/valsartan/hydrochlorothiazide (Exforge HCT), amlodipine/benazepril (Lotrel), amlodipine/medoxomil (Azor), olmesartan/amlodipine/hydrochlorothiazide (Tribenzor), and verapamil SR/trandolapril) were updated to replace the Pregnancy Category assignment with descriptive text; it can cause fetal harm when administered to a pregnant woman. The remaining medications that continue to use a Pregnancy Category assignment are categorized as Pregnancy Category D (amlodipine/perindopril [Prestalia].

Renal Impairment

Amlodipine/benazepril (Lotrel), amlodipine/olmesartan/HCTZ (Tribenzor), amlodipine/perindopril (Prestalia), and amlodipine/valsartan/HCTZ (Exforge HCT) are not recommended in patients with creatinine clearance (CrCl) < 30 mL/min. Patients with a CrCl of 30 to 80 mL/min should not exceed amlodipine/perindopril (Prestalia) doses of 7/5 mg.

There have been no studies of amlodipine/olmesartan (Azor) in patients with renal impairment; there are no specific dosage adjustment recommendations. No initial dose adjustment for amlodipine/telmisartan (Twynsta) is required in patients with mild to moderate renal impairment; however, doses should be titrated slowly in patients with severe renal impairment.

Use caution with amlodipine/valsartan (Exforge) when CrCl < 10 mL/min, although it has not been studied in severe renal impairment.

Verapamil SR/trandolapril should be dose adjusted if CrCl is < 30 mL/min.

Hepatic Impairment

Patients with hepatic impairment have decreased clearance of amlodipine and verapamil. Caution should be exercised when utilizing amlodipine-containing (Azor, Exforge, Exforge HCT, Lotrel, Prestalia, Tribenzor, Twynsta) or verapamil-containing products in patients with hepatic impairment. Slow titration may be appropriate. Amlodipine-containing products should be started at a dose of 2.5 mg of the amlodipine component and titrated slowly in this patient population. This strength is not an option with the combination products: Azor, Exforge, Exforge HCT, Tribenzor, or Twynsta. A dosage adjustment may be required for verapamil SR/trandolapril in patients with hepatic impairment.

Amlodipine/perindopril (Prestalia) is not recommended in patients with hepatic impairment.

Rarely, patients receiving ACE inhibitors may develop jaundice or marked elevations of hepatic enzymes. If this occurs, patients should discontinue the ACE inhibitor and receive appropriate medical follow-up.

Other Populations

African American patients receiving ACE inhibitor monotherapy have reported a higher incidence of angioedema compared to non-African Americans. In controlled clinical trials, ACE inhibitors have less effect on blood pressure in African American patients than in non-African Americans. Amlodipine/olmesartan (Azor) and amlodipine/olmesartan/HCTZ (Tribenzor) have shown to be effective in treating African American patients, with the magnitude of blood pressure reduction in African Americans approaching that observed in the non-African Americans population.

Elderly patients may be more sensitive to antihypertensive medications, even if the blood pressure effect is smaller than in younger patients, based on pharmacokinetic studies. When starting or adding amlodipine for patients at least 75 years old or patients with hepatic impairment, the recommended dose of amlodipine is 2.5 mg, due to impaired clearance. Doses of amlodipine/perindopril (Prestalia) exceeding 7/5 mg is not recommended in elderly patients.

DOSAGES[80,81,82,83,84,85,86,87]

Drug	Dosage	Combinations Available (Calcium Channel Blocker/Angiotensin Modulator)
amlodipine/benazepril (Lotrel)	1 daily	2.5/10 mg (generic only), 5/10 mg, 5/20 mg, 10/20 mg, 5/40 mg (generic only), 10/40 mg capsules
amlodipine/olmesartan (Azor)	1 daily	5/20 mg, 5/40 mg, 10/20 mg, 10/40 mg tablets
amlodipine/olmesartan/HCTZ (Tribenzor)	1 daily	5/20/12.5 mg, 5/40/12.5 mg, 5/40/25 mg, 10/40/12.5 mg, 10/40/25 mg tablets
amlodipine/perindopril (Prestalia)	1 daily	2.5/3 mg, 5/7 mg, 10/14 mg tablets
amlodipine/telmisartan (Twynsta)	1 daily	5/40 mg, 5/80 mg, 10/40 mg
amlodipine/valsartan (Exforge)	1 daily	5/160 mg, 5/320 mg, 10/160 mg, 10/320 mg tablets
amlodipine/valsartan/HCTZ (Exforge HCT)	1 daily	5/160/12.5 mg, 5/160/25 mg, 10/160/12.5 mg, 10/160/25 mg, 10/320/25 mg tablets
verapamil SR/trandolapril	1 daily	180/2 mg, 240/1 mg, 240/2 mg, 240/4 mg tablets

CLINICAL TRIALS

Search Strategy

Studies were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in the commercially available combinations for this category. Randomized, controlled trials comparing agents within this class for the treatment of hypertension are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship and/or funding must be considered, the studies in this review have also been evaluated for validity and importance.

amlodipine/benazepril (Lotrel) versus amlodipine (Norvasc®) and/or benazepril (Lotensin®)

In a multicenter, randomized, double-blind study, 448 patients were randomized to receive 1 of the following treatments for 8 weeks: 1) benazepril 10 mg plus placebo, 2) benazepril 10 mg plus amlodipine 2.5 mg, or 3) benazepril 10 mg plus amlodipine 5 mg.[88] Initially, patients underwent a 2-week placebo run-in phase followed by a 4-week benazepril 10 mg daily run-in phase and then underwent randomization if the mean diastolic blood pressure (DBP) was ≥ 95 mm Hg and < 120 mm Hg after 4 weeks of benazepril 10 mg daily. The 24-hour post-dose sitting and standing systolic BP (SBP) and DBP values were statistically lower with combination therapy than with benazepril 10 mg. The tolerability was good in the 3 treatment groups.

In a multicenter, double-blind, parallel-group study, 308 patients were randomized to 1 of the following treatments for 8 weeks: amlodipine 5 mg/benazepril 20 mg, amlodipine 5 mg, benazepril 20 mg, or placebo once daily for the treatment of hypertension.[89] The combination had a significantly greater reduction in blood pressure compared to the other monotherapies ($p<0.001$). A responder rate, as defined as DBP < 90 mm Hg or > 10 mm Hg decrease in mean sitting DBP, of 87% was observed for amlodipine/benazepril versus 67.5% for amlodipine, 53.3% for benazepril, and 15.8% for placebo ($p<0.005$). Edema occurred less often in the amlodipine/benazepril group than in the amlodipine group which has also been observed in other studies.[90]

A double-blind study compared the efficacy and safety of amlodipine 5 to 10 mg and benazepril 40 mg to benazepril 40 mg monotherapy in hypertensive patients (n=298) not controlled on benazepril 40 mg monotherapy.[91] Patients underwent a 2-week washout period and then started on benazepril 40 mg daily. Patients with a mean sitting DBP ≥ 95 mm Hg were randomized to amlodipine 5 mg (then amlodipine 10 mg after 4 weeks) in addition to benazepril 40 mg or to continue on benazepril 40 mg daily for 8 weeks. The mean reduction in sitting BP after 8 weeks compared to baseline was -5/-7 mm Hg with benazepril and -17/-14 mm Hg with amlodipine/benazepril ($p<0.0001$). Goal attainment of

target BP (DBP < 90 mm Hg) was achieved in 80% and 45% of amlodipine/benazepril and benazepril groups, respectively (p<0.0001). Both therapies were well tolerated.

A total of 364 patients with stage 2 hypertension were enrolled in a multicenter, double-blind, 12-week trial comparing the efficacy of amlodipine/benazepril combination and amlodipine monotherapy.[92] Patients were randomized to amlodipine/benazepril 5/20 mg daily and titrated to 10/20 mg daily or amlodipine 5 mg daily titrated to 10 mg daily. The combination therapy achieved a reduction in SBP of greater than -25 to -32 mm Hg in 74.2% of patients whereas, in the amlodipine group, only 53.9% of patients achieved the desired BP reductions (p<0.0001). Significantly more patients in the combination therapy group attained BP < 140/90 mm Hg (61%) compared to 43.3% in the monotherapy group (p=0.0007). A significant difference was also seen for those patients achieving a BP < 135/80 mm Hg (35.7% versus 19.1% of patients, respectively; p=0.0004). For patients with baseline SBP > 180 mm Hg, combination therapy had significantly greater reductions in SBP compared to monotherapy (-42.3 versus -30.4 mm Hg, p=0.001). Another study, SELECT, has been published with similar results.[93]

In a randomized, double-blind, multicenter, 12-week study, 70 hypertensive patients with at least 1 other endothelial dysfunction risk factor were assigned to amlodipine/benazepril 5/20 mg per day (force titrated to 5/40 mg per day) or amlodipine 5 mg per day (force titrated to 10 mg per day).[94] The study examined combination therapy versus monotherapy in modulating endothelial dysfunction. Both treatment arms resulted in significant median increases from baseline in percentage flow-mediated vasodilation (2% versus 1.2%, respectively), but between group differences were not statistically significant. Reductions in SBP (p=0.0452) and DBP (p=0.0297) were significantly greater with the combination therapy (-18.6/-12.3 mm Hg) versus monotherapy (-14.8/-9.1 mm Hg). A correlation between reduction in SBP and change in percentage of flow mediated vasodilation was seen only for combination therapy.

Amlodipine and benazepril were compared to each other and to the combination in a randomized, double-blind, placebo-controlled, multicenter trial.[95] A total of 454 adult patients with hypertension were randomized to amlodipine 5 mg, benazepril 10 mg, the combination, or placebo once daily for 8 weeks. The combination group had greater reductions in sitting DBP from baseline compared to amlodipine (p<0.03), benazepril, and placebo (both p<0.001). Heart rate did not differ among the groups. Edema was less in the combination group compared to amlodipine (1.7 versus 4.5%).

In a multicenter, double-blind, 8-week study, 111 Chinese patients with mild to moderate hypertension were randomized to amlodipine/benazepril 2.5/5 mg daily or amlodipine 5 mg daily.[96] Blood pressure was obtained after 4 weeks of therapy and then the dose was titrated up if BP was > 140/90 mm Hg. After 8 weeks of therapy, BP control rates were similar with 56% in the combination group and 46.2% in the amlodipine monotherapy group (p=0.32). Fixed-dose combination resulted in similar reductions in sitting SBP and DBP compared with monotherapy (SBP: -19.3 mm Hg versus -20.9 mm Hg; DBP: -9.2 mm Hg versus -11.3 mm Hg; both p=NS). Safety profiles did not differ between groups, but cough was more common in the combination group (11% versus 0; p=0.013).

amlodipine/olmesartan (Azor) versus olmesartan initial therapy

A randomized, double-blind, parallel-group, multicenter trial included patients with moderate to severe hypertension (≥ 160/100 mm Hg) and investigated the additional efficacy on BP reduction and BP goal rates (< 140/90 mm Hg for patients without diabetes mellitus, < 130/80 mm Hg for patients

with diabetes) when amlodipine 5 or 10 mg per day was added to olmesartan 20 mg/day in patients not adequately controlled on olmesartan alone.[97] After an 8-week open-label olmesartan 20 mg monotherapy period, 538 patients with BP ≥ 140/90 mm Hg were randomized to 8 weeks of olmesartan/placebo, olmesartan/amlodipine 20 mg/5 mg, or olmesartan/amlodipine 20 mg/10 mg. The adjusted mean change in seated DBP (SeDBP) from baseline was -7.6 mm Hg for olmesartan/placebo, -10.4 mm Hg for olmesartan/amlodipine 20 mg/5 mg (p=0.0006 versus olmesartan/placebo), and -10.9 mm Hg for olmesartan/amlodipine 20 mg/10 mg (p<0.0001 versus olmesartan/placebo). Mean changes in SeSBP from baseline with olmesartan/placebo, olmesartan/amlodipine 20 mg/5 mg, and olmesartan/amlodipine 20 mg/10 mg were -10.8, -16.1, and -16.7 mm Hg, respectively (p<0.0001 for both dose regimens versus olmesartan/placebo). BP goal rates were higher with olmesartan/amlodipine 20 mg/5 mg and olmesartan/amlodipine 20 mg/10 mg (44.5% and 45.8%, respectively; p=0.0011 and p=0.0004, respectively) versus olmesartan/placebo (28.5%). Combination therapy was well tolerated, and the incidence of drug-related adverse events was 8.9% for olmesartan/placebo, 7.7% for olmesartan/amlodipine 20 mg/5 mg, and 11.3% for olmesartan/amlodipine 20 mg/10 mg (p=0.49).

amlodipine/olmesartan (Azor) versus amlodipine (Norvasc) or olmesartan (Benicar®)

In a multicenter, randomized, double-blind trial, the efficacy and tolerability of the combination of olmesartan and amlodipine were compared to the individual components in 1,940 patients with hypertension.[98] Patients were either untreated or underwent a 2-week wash-out period and had a seated DBP of 95 – 120 mm Hg. The mean baseline BP was 164/102 mm Hg, and 79.3% of patients had stage 2 hypertension. Patients were randomized to olmesartan 10, 20, or 40 mg daily, amlodipine 5 or 10 mg daily, each possible combination of amlodipine/olmesartan, or placebo. The primary endpoint was the change from baseline in seated DBP after eight weeks of treatment. Combination therapy with amlodipine/olmesartan had dose-dependent reductions in seated DBP ranging from -13.8 mm Hg to -19 mm Hg. The secondary endpoint, seated SBP, reductions observed in the combination therapy group ranged from -23.6 mm Hg to -30.1 mm Hg. Both SBP and DBP reductions with the combination therapy were significantly greater than those observed with either monotherapy (p<0.001). The percentages of patients achieving BP goal attainment were significantly higher with combination therapy compared to monotherapy (p<0.005). Combination therapy was well tolerated. The most common adverse events were edema and headache. Percentages for edema ranged from 9.9% with olmesartan 20 mg to 36.8% with amlodipine 10 mg compared to 12.3% with placebo. Percentages of patients reporting headache ranged from 2.5% in the amlodipine/olmesartan 10-5 mg group to 8.7% in the olmesartan 20 mg group; a total of 14.2% of patients receiving placebo reported headache.

amlodipine/olmesartan/HCTZ (Tribenzor) versus amlodipine (Norvasc) or olmesartan (Benicar)

The antihypertensive efficacy of triple combination therapy with amlodipine/olmesartan/HCTZ was studied in a double-blind, active-controlled study in hypertensive patients (n=2,492).[99] Patients were randomized to receive olmesartan/amlodipine/HCTZ 40/10/25 mg, olmesartan/amlodipine 40/10 mg, olmesartan/HCTZ 40/25 mg, or amlodipine/HCTZ 10/25 mg for 2 to 4 weeks. Patients were then randomized to continue on the dual therapy they were receiving or to receive triple therapy. After 8 weeks of treatment, the triple combination therapy produced greater reductions in both systolic and diastolic blood pressures (p<0.0001) compared to each of the dual combination therapies. Reductions in seated blood pressure measures were: 8.4/4.5 mm Hg for HCTZ 25 mg added to olmesartan 40

mg/amlodipine 10 mg; 7.6/5.4 mm Hg for amlodipine 10 mg added to olmesartan 40 mg/HCTZ 25 mg; and 8.1/5.4 mm Hg for olmesartan 40 mg added to amlodipine 10 mg/HCTZ 25 mg. A total of 440 patients participated in the ambulatory blood pressure monitoring portion of the study. Over the 24-hour period, there was a greater reduction in diastolic and systolic ambulatory blood pressure for olmesartan/amlodipine/hydrochlorothiazide 40/10/25 mg compared to each of the dual combination therapies.

amlodipine/perindopril arginine (Prestalia) versus amlodipine (Norvasc) or perindopril erbumine (Aceon®)

In a double-blind, active controlled study a total of 837 hypertensive patients with a mean baseline blood pressure of 158/101 mm Hg received either the highest strength of amlodipine/perindopril arginine 10/14 mg, perindopril erbumine 16 mg, or amlodipine 10 mg once daily for 6 weeks.[100] Overall, 20% of the population had type 2 diabetes and 34% were African American. At Week 6, amlodipine/perindopril arginine 10/14 mg resulted in statistically significantly greater reductions in blood pressure than each monotherapy. The reductions in blood pressure with the combination product were 10.1/6.3 mm Hg greater than with perindopril erbumine 16 mg and 3.9/2.5 mm Hg greater than with amlodipine 10 mg. Treatment with amlodipine/perindopril arginine 10/14 mg did not provide additional blood pressure reductions beyond that achieved with use of amlodipine 10 mg in African American patients and in diabetic patients.

The lowest strength of amlodipine/perindopril arginine was studied in 246 hypertensive patients with a mean baseline blood pressure of 161/101 mm Hg.[101] Patients received amlodipine/perindopril arginine 2.5 /3.5 mg, perindopril arginine 3.5 mg, perindopril arginine 5 mg, amlodipine 2.5 mg, amlodipine 5 mg, or placebo. No patients in the study had diabetes and 1% was African American. At Week 8, amlodipine/perindopril arginine 2.5 /3.5 mg resulted in statistically significantly greater reductions in blood pressure than perindopril arginine 3.5 mg and amlodipine 2.5 mg. The reduction in blood pressure with amlodipine/perindopril arginine 2.5 /3.5 mg was 7.2/4.1 mm Hg greater than with placebo.

amlodipine/telmisartan (Twynsta) versus amlodipine (Norvasc) or telmisartan (Micardis®)

A randomized 4 x 4 factorial study evaluated the efficacy and safety of telmisartan plus amlodipine in 1,461 patients with stage 1 or 2 hypertension (BP 153.2 ± 12.1/101.7 ± 4.3 mm Hg).[102] Patients were randomized to one of 16 treatment groups using combinations of dose ranges of telmisartan 0 to 80 mg and amlodipine of 0 to 10 mg daily for 8 weeks. Blood pressure reductions were greater with combination therapy than respective monotherapies, with the greatest mean systolic/diastolic BP reductions seen in the telmisartan 80 mg plus amlodipine 10 mg group (-26.4/-20.1 mm Hg; $p<0.05$ compared with both monotherapies). BP control was also greatest in the telmisartan 80 mg/amlodipine 10 mg group (76.5% [overall control] and 85.3% [DBP control]), and BP response rates were more than 90% with this combination. Peripheral edema was most common in the amlodipine 10 mg group (17.8%); however, this rate was notably lower when amlodipine was used in combination with telmisartan: 11.4% (telmisartan 20 mg/amlodipine 10 mg), 6.2% (telmisartan 40 mg/ amlodipine 10 mg, and 11.3% (telmisartan 80 mg/amlodipine 10 mg).

A placebo-controlled, double-blind, 4 x 4 factorial design trial in 562 patients with clinic diastolic BP at least 95 and 119 mm Hg or less were randomized to receive telmisartan 0, 20, 40, or 80 mg and/or

amlodipine 0, 2.5, 5, or 10 mg.[103] Ambulatory BP monitoring was performed at baseline and after 8 weeks of treatment; the endpoints of interest were the changes from baseline in 24-h systolic and diastolic BP. Secondary endpoints included the proportion of responders (≥ 10 mm Hg BP reduction from baseline and/or < 130/80 mm Hg mean 24-h BP) and controlled patients (< 130/80 mm Hg mean 24-h BP). Combination therapies of telmisartan and amlodipine lowered 24-h BP to a larger extent than the corresponding monotherapies at all doses. Mean reductions from baseline in 24-h BP for the combination of the highest doses of telmisartan 80 mg and amlodipine 10 mg were -22.4/-14.6 mm Hg versus -11.9/-6.9 mm Hg for amlodipine 10 mg and -11/-6.9 mm Hg for telmisartan 80 mg ($p<0.0001$ for each comparison). In addition, BP response and control rates (24-h BP < 130/80 mm Hg) were significantly higher with the combination therapy versus the monotherapy groups.

Patients (n=1,078) with a DBP ≥ 100 mm Hg at baseline were included in a subgroup analysis of the above study.[104] The primary endpoint was the change in the in-clinic seated trough cuff DBP from baseline to study end for combination versus respective monotherapies. Secondary endpoints included the change in the in-clinic seated trough SBP, BP response, and control rates. In-clinic DBP and SBP reductions were greater with combination therapies than respective monotherapies, with the greatest least-square mean SBP/DBP reductions (-26.5 ± 1.2/-21 ± 0.8 mm Hg) observed in the telmisartan 80 mg plus amlodipine 10 mg group; 77% and 85% of patients in this treatment group achieved BP control (< 140/90 mm Hg) and DBP control (< 90 mm Hg), respectively. Peripheral edema was reported in 17.2% of patients in the amlodipine 10 mg group; however, this was substantially lower when telmisartan was used in combination: 7% (telmisartan 40 mg/amlodipine 10 mg) and 9.5% (telmisartan 80 mg/ amlodipine 10 mg).

amlodipine/valsartan (Exforge) versus amlodipine (Norvasc) or valsartan (Diovan®)

Efficacy of the combination of amlodipine and valsartan were compared to the individual components in 2 multicenter, 8-week, randomized, double-blind, parallel-group trials.[105] In the first study, 1,911 patients were randomized to receive amlodipine 2.5 or 5 mg once daily, valsartan 40 to 320 mg once daily, or the combination of amlodipine 2.5 or 5 mg plus valsartan 40 to 320 mg once daily, or placebo for 8 weeks. In the second study, 1,250 patients were randomized to amlodipine 10 mg once daily, valsartan 160 or 320 mg once daily, or the combination of amlodipine 10 mg with valsartan 160 or 320 mg once daily, or placebo for 8 weeks. The primary efficacy parameter was the change from baseline in mean sitting DBP at the end of the study. A positive dose response was observed for all combinations. With the exception of a few combinations that included amlodipine 2.5 mg, the combination regimens in both studies were associated with significantly greater reductions in mean sitting DBP and mean sitting SBP compared with their individual components and placebo ($p<0.05$). The highest response rate, defined as patients achieving mean sitting DBP < 90 mm Hg or > 10 mm Hg decrease from baseline, in the first study was associated with the highest dose of combination therapy (amlodipine 5 mg/valsartan 320 mg: 91.3%). Amlodipine 5 mg, valsartan 320 mg, and placebo were associated with response rates of 71.9%, 73.4%, and 40.9%, respectively. In the second study, the response rates were similar for the 2 doses of combination therapy (amlodipine 10 mg/valsartan 160 mg: 88.5%; amlodipine 10 mg/valsartan 320 mg: 87.5%). Amlodipine 10 mg was associated with a response rate of 86.9%; valsartan 160 and 320 mg were associated with response rates of 74.9% and 72%, respectively; and placebo was associated with a response rate of 49.3%. Peripheral edema was reported less frequently with the combination therapy than with amlodipine monotherapy (5.4% versus 8.7%, respectively; $p=0.014$). Combination therapy had a significantly higher incidence of peripheral edema

compared to valsartan monotherapy (5.4% versus 2.1%, respectively; p<0.001) but not significantly different than placebo (3%).

amlodipine/valsartan (Exforge)

In a randomized, double-blind, multicenter study, 894 patients whose blood pressure was uncontrolled by monotherapy were switched to amlodipine/valsartan 5/160 mg or 10/160 mg.[106] After 16 weeks, BP control (BP < 140/90 mm Hg or < 130/80 mm Hg for diabetics) was achieved in 72.7% (95% CI, 68.6 to 76.9) of patients receiving amlodipine/valsartan 5/160 mg and in 74.8% (95% CI, 70.8 to 78.9) receiving amlodipine/valsartan 10/160 mg. Incremental reductions from baseline in mean sitting systolic and diastolic BP were significantly greater with the higher dose (20+/-0.7 versus 17.5 ± 0.7 mm Hg, p=0.0003 and 11.6 ± 0.4 versus 10.4 ± 0.4 mm Hg, p=0.0046). Peripheral edema was the most frequent adverse event.

A multicenter, randomized, double-blind, active-controlled study in patients with essential hypertension was conducted to demonstrate additional BP-lowering effects of amlodipine/valsartan combination in patients whose BP was not adequately controlled on valsartan alone.[107] After a washout period followed by a single-blind valsartan 160 mg run-in period, patients with mean sitting DBP ≥ 90 mm Hg and < 110 mm Hg were randomized to receive amlodipine/valsartan (10/160 mg or 5/160 mg) or valsartan 160 mg for 8 weeks. The primary efficacy variable was change from baseline in mean DBP at study end. Secondary efficacy variables included change from baseline in mean sitting SBP, responder rate (mean DBP < 90 mm Hg or ≥ 10 mm Hg reduction from baseline), and DBP control rate (mean DBP < 90 mm Hg). Of 1,136 patients enrolled in the single-blind phase, 947 (mean age: 54.6 years) were randomized. Greater reductions in mean SBP/DBP were observed in both amlodipine/valsartan combinations (10/160 mg: 14.3/11.5 mm Hg, 5/160 mg: 12.2/9.6 mm Hg; both p<0.0001) compared to valsartan 160 mg (8.3/6.7 mm Hg). Responder rates were higher in both combination therapy groups (10/160 mg: 81% [p<0.0001]; 5/160 mg: 68% [p=0.0018], respectively) compared to monotherapy (57%). Peripheral edema was the most frequent adverse event reported in amlodipine/valsartan 10/160 mg (9.1%), 5/160 mg (0.9%), and valsartan 160 mg (1.3%).

amlodipine/valsartan (Exforge) versus amlodipine as initial therapy

Two double-blind, active-controlled studies were conducted in which the combination of amlodipine/valsartan was administered as initial therapy.[108] In one study, a total of 572 African American patients with moderate to severe hypertension were randomized to receive either combination amlodipine/valsartan or amlodipine monotherapy for 12 weeks. The initial dose of amlodipine/valsartan was 5/160 mg for 2 weeks with forced titration to 10/160 mg for 2 weeks, followed by optional titration to 10/320 mg for four weeks and optional addition of HCTZ 12.5 mg for 4 weeks. The initial dose of amlodipine was 5 mg for 2 weeks with forced titration to 10 mg for 2 weeks, followed by optional titration to 10 mg for 4 weeks and optional addition of HCTZ 12.5 mg for 4 weeks. At the primary endpoint of 8 weeks, the treatment difference between amlodipine/valsartan and amlodipine was 6.7/2.8 mm Hg in favor of the combination product.

In the other study of similar design, a total of 646 patients with moderate to severe hypertension (SBP of ≥ 160 mm Hg and < 200 mm Hg) were randomized to receive either combination amlodipine/valsartan or amlodipine monotherapy for 8 weeks.[109] The initial dose of amlodipine/valsartan was 5/160 mg for 2 weeks with forced titration to 10/160 mg for 2 weeks, followed by the optional addition of HCTZ 12.5 mg for 4 weeks. The initial dose of amlodipine was 5 mg

for 2 weeks with forced titration to 10 mg for 2 weeks followed by the optional addition of HCTZ 12.5 mg for 4 weeks. At the primary endpoint of 4 weeks, the treatment difference between amlodipine/valsartan and amlodipine was 6.6/3.9 mm Hg in favor of the combination product.

This multicenter, randomized, double-blind, active-controlled study evaluated the efficacy and tolerability of amlodipine/valsartan combination therapy in patients with essential hypertension (n=944) who were not adequately controlled on amlodipine monotherapy.[110] Patients with mean sitting diastolic blood pressure (msDBP) ≥ 90 mm Hg and < 110 mm Hg were randomized to receive amlodipine/valsartan 10/160 mg (n=473) or amlodipine 10 mg (n=471) for 8 weeks after a washout period followed by a single-blind amlodipine 10 mg run-in period. The primary efficacy variable was change from baseline in msDBP at study endpoint. Secondary endpoints were change from baseline in mean sitting systolic blood pressure (msSBP), responder rate (msDBP < 90 mm Hg or ≥ 10 mm Hg reduction from baseline), and DBP control rate (msDBP < 90 mm Hg). Combination therapy resulted in greater reductions (p<0.0001) from baseline in msSBP/msDBP (12.9/11.4 mm Hg) compared to monotherapy (10/9.3 mm Hg). Responder rate was significantly greater (p=0.0011) with combination therapy (79%) compared to monotherapy (70.1%), and the percentage of patients with controlled DBP was also higher (p<0.0001) with combination therapy (77.8%) compared to monotherapy (66.5%). The incidence of peripheral edema was slightly higher with amlodipine monotherapy (9.4%) compared to combination therapy (7.6%).

verapamil SR/trandolapril and trandolapril (Mavik®) and/or verapamil SR

In a randomized, double-blind placebo-controlled trial, trandolapril, verapamil SR, the combination of the 2 agents, and placebo were evaluated for antihypertensive efficacy in 631 adults with hypertension.[111] Both single agent groups lowered BP more than placebo. The combination lowered BP more than either agent alone. All groups had similar adverse events, and therapies were well tolerated. Two other prospective, double-blind trials found similar results.[112,113]

The antihypertensive efficacy of verapamil SR and trandolapril were evaluated in 438 patients with high normal BP or borderline isolated systolic hypertension and type 2 diabetes.[114] The patients were randomized to verapamil SR plus trandolapril, trandolapril, or placebo and followed for 16 weeks in a double-blind fashion. Doses were doubled if BP goals were not achieved after 8 weeks (<130/85 mm Hg). Both active treatment groups significantly lowered BP compared to placebo (both p<0.001). However, no significant difference in the control of SBP was seen between the 2 active treatment groups. The percentage of patients achieving BP < 130/85 mm Hg was 36.5% in the trandolapril group, 37.8% in the combination group, and 14.9% in the placebo group (p=0.009, combination and trandolapril groups versus placebo). Control rate for DBP (< 85 mm Hg) was significantly higher in the combination group (88.8%) when compared with trandolapril (79.1%) or placebo (63.5%; p=0.002). Withdrawal rates were similar in all groups.

The BENEDICT study assessed trandolapril and verapamil, alone or in combination, for efficacy in preventing microalbuminuria in 1,204 patients with hypertension, type 2 diabetes, and normal urinary albumin excretion.[115] Patients were randomized to 3 years of trandolapril 2 mg daily plus verapamil SR 180 mg daily, trandolapril 2 mg daily, verapamil SR 240 mg daily, or placebo in a double-blind fashion. The primary outcome was the development of microalbuminuria (>20 mcg/min at 2 visits). Microalbuminuria was observed in 5.7% of the combination group, 6% in trandolapril monotherapy, 11.9% in verapamil monotherapy, and 10% in the placebo group. Trandolapril plus verapamil and

trandolapril monotherapy reduced the risk of the development of microalbuminuria to a similar extent and greater than placebo. Verapamil was similar to placebo.

The INVEST trial compared the combination of verapamil SR and trandolapril with atenolol and hydrochlorothiazide in 22,576 hypertensive coronary artery disease (CAD) patients over 50 years old.[116] In the randomized, open-label, blinded endpoint, multinational trial, patients were randomized to verapamil SR or atenolol. After a mean follow-up of 2.7 years, the occurrence of all-cause death, nonfatal myocardial infarction (MI) or nonfatal stroke, and BP control and goal attainment were similar in both groups. While the study did not specifically provide the combination tablet form of verapamil SR and trandolapril, INVEST did provide efficacy information regarding the co-administration of verapamil SR and trandolapril in a large clinical trial.

A subgroup of patients without diabetes from the randomized, double-blinded INVEST trial at study entry were investigated for newly diagnosed diabetes during follow-up.[117] Newly diagnosed diabetes was less frequent in the verapamil SR versus atenolol group (7% versus 8.2%; hazard ratio [HR] 0.85; 95% CI, 0.76 to 0.95; p<0.01). Some of the characteristics of risk for newly diagnosed diabetes included United States residence, left ventricular hypertrophy, previous stroke/transient ischemic attack, and Hispanic ethnicity. Addition of trandolapril to verapamil SR decreased diabetes risk and addition of hydrochlorothiazide to atenolol increased the diabetes risk.

Another substudy of INVEST evaluated 7,218 patients with prior MI for the primary outcome of time to first occurrence of death (all-cause), nonfatal MI, or nonfatal stroke.[118] Secondary outcomes included death, total MI (fatal and nonfatal), and total stroke (fatal and nonfatal) considered separately. During the 2.8 ± 1 years of follow-up, patients assigned to the verapamil-SR-based and atenolol-based groups had comparable blood pressure control, and the incidence of the primary outcome was equivalent. There was no difference between the 2 groups for the outcomes of either death or total MI. More patients reported excellent/good well-being (82.3% versus 78%, p=0.02) at 24 months with a trend toward less incidence of angina pectoris (12% versus 14.3%, adjusted p=0.07), nonfatal stroke (1.4% versus 2%; p=0.06), and total stroke (2% versus 2.5%, p=0.18) in the verapamil-SR-based group. In this study of hypertensive patients with prior MI, a verapamil SR-based group was equivalent to a beta-blocker-based group for blood pressure control and prevention of cardiovascular events.

META-ANALYSIS

A meta-analysis of 17 randomized controlled trials including 3,291 patients found that the combination treatment of amlodipine and ACE inhibitors resulted in a greater reduction of both systolic blood pressure (SBP) (weighted mean difference [WMD], 5.72; 95% CI, 4.1 to 7.33) and diastolic blood pressure (DBP) (WMD, 3.62; 95% CI, 4.85 to 2.39) than monotherapy.[119] The combination treatment also generated significantly greater reductions for the mean ambulatory SBP and DBP during the full 24 hours (WMD: SBP, 4.24 [95% CI, 6.82 to 1.67]; DBP, 2.23 [95% CI, 3.73 to 0.69]), but not for the trough (WMD: SBP, 4.52, [95% CI, 9.56 to -0.51]; DBP, 3.7, [95% CI, 7.65 to -0.25]). The hypertension therapeutic control (SBP < 140 mm Hg, DBP < 90 mm Hg) rate for the combination treatment is higher than that for monotherapy (relative risk [RR], 1.36; 95% CI, 1.07 to 1.73). The combination treatment also resulted in a lower overall rate of adverse events (RR, 0.86; 95% CI, 0.75 to 0.99) and edema (RR, 0.4; 95% CI, 0.29 to 0.56), but a higher rate of cough (RR, 3.28; 95% CI, 2.03 to 5.29) as compared with monotherapy.

SUMMARY

Most patients require more than a single medication to achieve adequate blood pressure control. The combinations of an angiotensin modulator with a calcium channel blocker or a beta blocker have been shown to be more effective than either agent alone for the treatment of hypertension. The combination products appear similar in efficacy and safety; however, comparative trials are lacking.

REFERENCES

1 Lotrel [package insert]. East Hanover, NJ; Novartis; April 2021.
2 Azor [package insert]. Parsippany, NJ; Daiichi-Sankyo; October 2020.
3 Tribenzor [package insert]. Parsippany, NJ; Daiichi-Sankyo; October 2020.
4 Prestalia [package insert]. Cincinnati, OH; Symplmed; August 2019.
5 Twynsta [package insert]. Ridgefield, CT; Boehringer Ingelheim; November 2018.
6 Exforge [package insert]. East Hanover, NJ; Novartis; April 2021.
7 Exforge HCT [package insert]. East Hanover, NJ; Novartis; February 2021.
8 Trandolapril/verapamil [package insert]. Mahwah, NJ; Glenmark; September 2019.
9 Center for Disease Control and Prevention (CDC). Facts about hypertension. Last updated September 27, 2021. Available at: https://www.cdc.gov/bloodpressure/facts.htm. Accessed December 3, 2021.
10 Fuchs FD, Whelton PK. Higher blood pressure and cardiovascular disease. Hypertension. 2020;75(2):285-292. DOI: 10.1161/HYPERTENSIONAHA.119.14240.
11 Screening for hypertension in adults. US Preventive Services Task Force Reaffirmation Recommendation Statement. 2021. Available at: https://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/high-blood-pressure-in-adults-screening. Accessed December 2, 2021.
12 James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the eighth joint national committee (JNC 8). JAMA. 2014; 311(5):507-520. DOI:10.1001/jama.2013.284427. Available at: http://jama.jamanetwork.com/article.aspx?articleid=1791497. Accessed December 2, 2021.
13 The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs. diuretic. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). JAMA. 2002; 288:2981-2997.
14 Qaseem A, Wilt TJ, Rich R, et al. Pharmacology treatment of hypertension in adults aged 60 years or older to higher versus lower blood pressure targets: a clinical practice guideline from the American College of Physicians and the American Academy of Family Physicians – 2017. Available at: https://www.acponline.org/clinical-information/guidelines. Accessed December 2, 2021.
15 Carey RM, Whelton PK, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: Executive summary. Hypertension. 2018;71:e13–e115. Available at https://professional.heart.org/professional/GuidelinesStatements/UCM_316885_Guidelines-Statements.jsp. Accessed December 2, 2021.
16 Jones DW, Whelton PK, et al. Management of stage 1 hypertension in adults with a low 10-year risk for cardiovascular disease: Filling a guidance gap: A Scientific Statement From the American Heart Association. Hypertension. 2021;77:e58-e67. Available at: https://professional.heart.org/en/guidelines-and-statements/guidelines-and-statements-search. Accessed December 2, 2021.
17 Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease. Circulation. 2019;140:e596–e646. DOI: 10.1161/CIR.0000000000000678. Available at: https://www.ahajournals.org/doi/pdf/10.1161/CIR.0000000000000678. Accessed December 2, 2021.
18 Casey Jr. DE, Thomas RJ, Bhalla V, et al. 2019 AHA/ACC clinical performance and quality measures for adults with high blood pressure: a report of the American College of Cardiology/American Heart Association task Force on performance measures. Circulation: Cardiovascular Quality and Outcomes. 2019;12:e000057. Available at: https://www.ahajournals.org/doi/10.1161/HCQ.0000000000000057. Accessed December 2, 2021.
19 Carey RM, Whelton PK, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: executive summary. Hypertension. 2018;71:e13–e115. Available at https://professional.heart.org/professional/GuidelinesStatements/UCM_316885_Guidelines-Statements.jsp. Accessed December 2, 2021.
20 American Diabetes Association. Cardiovascular disease and risk management: standards of medical care in diabetes–2021. Diabetes Care 2021;44 (Suppl. 1):S125–S150. DOI: 10.2337/dc21-S010. Available at: https://professional.diabetes.org/content-page/practice-guidelines-resources. Accessed December 2, 2021.
21 Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group. Clinical practice guidelines for diabetes management in chronic kidney disease. 2020. Kidney Int. 2020; 98 (4S): S1–S115. DOI: 10.1016/j.kint.2020.06.019. Available at: https://kdigo.org/guidelines/diabetes-ckd/. Accessed December 2, 2021.
22 Kidney Disease: Executive summary of the KDIGO 2021 Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease. Kidney Int. 2021; 99 (3): P559-569. DOI: 10.1016/j.kint.2020.10.026. Available at: https://www.kidney-international.org/article/S0085-2538(20)31269-2/fulltext. Accessed December 2, 2021.
23 Mehta LS, Watson KE, Barac A, et al.; Cardiovascular disease and breast cancer: where these entities intersect: a scientific statement from the American Heart Association. Circulation. 2018;137:e30–e66. DOI: 10.1161/CIR.0000000000000556. Available at:
https://professional.heart.org/professional/GuidelinesStatements/UCM_316885_Guidelines-Statements.jsp. Accessed December 2, 2021.
24 Muntner P, Shimbo D, Carey RM, et al; Measurement of blood pressure in humans: A scientific statement from the American Heart Association. American Heart Association. Hypertension. 2019;73:e35–e66. Available at: https://www.ahajournals.org/doi/10.1161/HYP.0000000000000087. Accessed December 2, 2021.

25 Lotrel [package insert]. East Hanover, NJ; Novartis; April 2021.
26 Azor [package insert]. Parsippany, NJ; Daiichi-Sankyo; October 2020.
27 Tribenzor [package insert]. Parsippany, NJ; Daiichi-Sankyo; October 2020.
28 Prestalia [package insert]. Cincinnati, OH; Symplmed; August 2019.
29 Twynsta [package insert]. Ridgefield, CT; Boehringer Ingelheim; November 2018.
30 Exforge [package insert]. East Hanover, NJ; Novartis; April 2021.
31 Exforge HCT [package insert]. East Hanover, NJ; Novartis; February 2021.
32 Trandolapril/verapamil [package insert]. Mahwah, NJ; Glenmark; September 2019.
33 DRUGDEX® System [Internet database]. Greenwood Village, CO: Thomson Micromedex. Updated periodically. https://www.micromedexsolutions.com/micromedex2/librarian/ssl/true. Accessed December 2, 2021.
34 Lotrel [package insert]. East Hanover, NJ; Novartis; April 2021.
35 Azor [package insert]. Parsippany, NJ; Daiichi-Sankyo; October 2020.
36 Tribenzor [package insert]. Parsippany, NJ; Daiichi-Sankyo; October 2020.
37 Prestalia [package insert]. Cincinnati, OH; Symplmed; August 2019.
38 Twynsta [package insert]. Ridgefield, CT; Boehringer Ingelheim; November 2018.
39 Exforge [package insert]. East Hanover, NJ; Novartis; April 2021.
40 Exforge HCT [package insert]. East Hanover, NJ; Novartis; February 2021.
41 DRUGDEX® System [Internet database]. Greenwood Village, CO: Thomson Micromedex. https://www.micromedexsolutions.com/micromedex2/librarian/ssl/true. Accessed December 2, 2021.
42 Trandolapril/verapamil [package insert]. Mahwah, NJ; Glenmark; September 2019.
43 Lotrel [package insert]. East Hanover, NJ; Novartis; April 2021.
44 Azor [package insert]. Parsippany, NJ; Daiichi-Sankyo; October 2020.
45 Tribenzor [package insert]. Parsippany, NJ; Daiichi-Sankyo; October 2020.
46 Prestalia [package insert]. Cincinnati, OH; Symplmed; August 2019.
47 Twynsta [package insert]. Ridgefield, CT; Boehringer Ingelheim; November 2018.
48 Exforge [package insert]. East Hanover, NJ; Novartis; April 2021.
49 Exforge HCT [package insert]. East Hanover, NJ; Novartis; February 2021.
50 Trandolapril/verapamil [package insert]. Mahwah, NJ; Glenmark; September 2019.
51 Food and Drug Administration. FDA drug safety communication: FDA review of cardiovascular risks for diabetics taking hypertension drug olmesartan not conclusive; label updates required. June 14, 2014. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm402323.htm. Accessed December 2, 2021.
52 Food and Drug Administration. FDA drug safety communication: Ongoing safety review of the angiotensin receptor blockers and cancer. June 2, 2011. http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm218845.htm. Accessed December 2, 2021.
53 Food and Drug Administration. FDA drug safety communication: No increase in risk of cancer with certain blood pressure drugs--Angiotensin Receptor Blockers (ARBs) July 15, 2010. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm257516.htm. Accessed December 2, 2021.
54 Bangalore S, Kumar S, Kjeldsen SE, et al. Antihypertensive drugs and risk of cancer: network meta-analyses and trial sequential analyses of 324,168 participants from randomised trials. The Lancet Oncology, 2011; 12(1):65-82. DOI: 10.1016/S1470-2045(10)70260-6.
55 Food and Drug Administration. FDA drug safety communication: FDA approves label changes to hydrochlorothiazide to describe small risk of non-melanoma skin cancer. August 20, 2020. Available at: https://www.fda.gov/drugs/drug-safety-and-availability/fda-approves-label-changes-hydrochlorothiazide-describe-small-risk-non-melanoma-skin-cancer. Accessed December 2, 2021
56 Lotrel [package insert]. East Hanover, NJ; Novartis; April 2021.
57 Azor [package insert]. Parsippany, NJ; Daiichi-Sankyo; October 2020.
58 Tribenzor [package insert]. Parsippany, NJ; Daiichi-Sankyo; October 2020.
59 Prestalia [package insert]. Cincinnati, OH; Symplmed; August 2019.
60 Twynsta [package insert]. Ridgefield, CT; Boehringer Ingelheim; November 2018.
61 Exforge [package insert]. East Hanover, NJ; Novartis; April 2021.
62 Exforge HCT [package insert]. East Hanover, NJ; Novartis; February 2021.
63 Trandolapril/verapamil [package insert]. Mahwah, NJ; Glenmark; September 2019.
64 Lotrel [package insert]. East Hanover, NJ; Novartis; April 2021.
65 Azor [package insert]. Parsippany, NJ; Daiichi-Sankyo; October 2020.
66 Tribenzor [package insert]. Parsippany, NJ; Daiichi-Sankyo; October 2020.
67 Prestalia [package insert]. Cincinnati, OH; Symplmed; August 2019.
68 Twynsta [package insert]. Ridgefield, CT; Boehringer Ingelheim; November 2018.
69 Exforge [package insert]. East Hanover, NJ; Novartis; April 2021.
70 Exforge HCT [package insert]. East Hanover, NJ; Novartis; February 2021.
71 Trandolapril/verapamil [package insert]. Mahwah, NJ; Glenmark; September 2019.
72 Lotrel [package insert]. East Hanover, NJ; Novartis; April 2021.
73 Azor [package insert]. Parsippany, NJ; Daiichi-Sankyo; October 2020.
74 Tribenzor [package insert]. Parsippany, NJ; Daiichi-Sankyo; October 2020.
75 Prestalia [package insert]. Cincinnati, OH; Symplmed; August 2019.
76 Twynsta [package insert]. Ridgefield, CT; Boehringer Ingelheim; November 2018.
77 Exforge [package insert]. East Hanover, NJ; Novartis; April 2021.
78 Exforge HCT [package insert]. East Hanover, NJ; Novartis; February 2021.
79 Trandolapril/verapamil [package insert]. Mahwah, NJ; Glenmark; September 2019.
80 Lotrel [package insert]. East Hanover, NJ; Novartis; April 2021.
81 Azor [package insert]. Parsippany, NJ; Daiichi-Sankyo; October 2020.
82 Tribenzor [package insert]. Parsippany, NJ; Daiichi-Sankyo; October 2020.

83 Prestalia [package insert]. Cincinnati, OH; Symplmed; August 2019.
84 Twynsta [package insert]. Ridgefield, CT; Boehringer Ingelheim; November 2018.
85 Exforge [package insert]. East Hanover, NJ; Novartis; April 2021.
86 Exforge HCT [package insert]. East Hanover, NJ; Novartis; February 2021.
87 Trandolapril/verapamil [package insert]. Mahwah, NJ; Glenmark; September 2019.
88 Fogari R, Corea L, Cardoni O, et al. Combined therapy with benazepril and amlodipine in the treatment of hypertension inadequately controlled by an ACE inhibitor alone. J Cardiovasc Pharmacol. 1997; 30:497-503.
89 Kuschnir E, Acuna E, Sevilla D, et al. Treatment of patients with essential hypertension: amlodipine 5mg/benazepril 20 mg compared with amlodipine 5mg, benazepril 20mg and placebo. Clin Ther. 1996; 18:1213-1224.
90 Fogari R, Malamani GD, Zoppi A, et al. Effect of benazepril addition to amlodipine on ankle oedema and subcutaneous tissue pressure in hypertensive patients. J Hum Hypertens. 2003; 17(3):207-212.
91 Chrysant SG, Bakris GL. Amlodipine/benazepril combination therapy for hypertensive patients nonresponsive to benazepril monotherapy. Am J Hypertens. 2004; 17(7):590-596.
92 Jamerson KA, Nwose O, Jean-Louis L, et al. Initial angiotensin-converting enzyme inhibitor/calcium channel blocker combination therapy achieves superior blood pressure control compared with calcium channel blocker monotherapy in patients with stage 2 hypertension. Am J Hypertens. 2004; 17(6):495-501.
93 Neutel JM, Smith DH, Weber MA, et al. Efficacy of combination therapy for systolic blood pressure in patients with severe systolic hypertension: the Systolic Evaluation of Lotrel Efficacy and Comparative Therapies (SELECT) study. J Clin Hypertens. 2005; 7(11):641-646.
94 Mohler ER 3rd, Herrington D, Ouyang P, et al. EXPLORE Investigators. A randomized, double-blind trial comparing the effects of amlodipine besylate/benazepril HCl vs. amlodipine on endothelial function and blood pressure. J Clin Hypertens (Greenwich). 2006; 8(10):692-698.
95 Pool J, Kaihlanen P, Lewis G, et al. Once-daily treatment of patients with hypertension: a placebo-controlled study of amlodipine and benazepril vs. amlodipine or benazepril alone. J Hum Hypertens. 2001; 15(7):495-498.
96 Ueng KC, Lin LC, Voon WC, et al. An eight-week, multicenter, randomized, double-blind study to evaluate the efficacy and tolerability of fixed-dose amlodipine/benazepril combination in comparison with amlodipine as first-line therapy in Chinese patients with mild to moderate hypertension. Blood Press Suppl. 2008; 1:24-131.
97 Barrios V, Brommer P, Haag U, et al. Olmesartan medoxomil plus amlodipine increases efficacy in patients with moderate-to-severe hypertension after monotherapy: a randomized, double-blind, parallel-group, multicentre study. Clin Drug Investig. 2009; 29(7):427-439.
98 Chrysant SG, Melino M, Karki S, et al. The combination of olmesartan medoxomil and amlodipine besylate in controlling high blood pressure: COACH, a randomized, double-blind, placebo-controlled, 8-week factorial efficacy and safety study. Clin Ther. 2008; 30(4):587-604.
99 Tribenzor [package insert]. Parsippany, NJ; Daiichi-Sankyo; October 2020.
100 Prestalia [package insert]. Cincinnati, OH; Symplmed; August 2019.
101 Prestalia [package insert]. Cincinnati, OH; Symplmed; August 2019.
102 Littlejohn TW 3rd, Majul CR, Olvera R, et al. Results of treatment with telmisartan-amlodipine in hypertensive patients. J Clin Hypertens (Greenwich). 2009; 11(4):207-213.
103 White WB, Littlejohn TW, Majul CR, Effects of telmisartan and amlodipine in combination on ambulatory blood pressure in stages 1-2 hypertension. Blood Press Monit. 2010; 15(4):205-12.
104 Littlejohn TW 3rd, Majul CR, Olvera R, et al. Telmisartan plus amlodipine in patients with moderate or severe hypertension: results from a subgroup analysis of a randomized, placebo-controlled, parallel-group, 4 x 4 factorial study. Postgrad Med. 2009; 121(2):5-14.
105 Philipp T, Smith TR, Glazer R, et al. Two multicenter, 8-week, randomized, double-blind, placebo-controlled, parallel-group studies evaluating the efficacy and tolerability of amlodipine and valsartan in combination and as monotherapy in adult patients with mild to moderate essential hypertension. Clin Ther. 2007; 29(4):563-580.
106 Allemann Y, Fraile B, Lambert M, et al. Efficacy of the combination of amlodipine and valsartan in patients with hypertension uncontrolled with previous monotherapy: the Exforge in Failure after Single Therapy (EX-FAST) study. J Clin Hyperten. 2008; 10(3):185-194.
107 Sinkiewicz W, Glazer RD, Kavoliuniene A, et al. Efficacy and tolerability of amlodipine/valsartan combination therapy in hypertensive patients not adequately controlled on valsartan monotherapy. Curr Med Res Opin. 2009; 25(2):315-324.
108 Exforge [package insert]. East Hanover, NJ; Novartis; April 2021.
109 Exforge [package insert]. East Hanover, NJ; Novartis; April 2021.
110 Schunkert H, Glazer RD, Wernsing M, et al. Efficacy and tolerability of amlodipine/valsartan combination therapy in hypertensive patients not adequately controlled on amlodipine monotherapy. Curr Med Res Opin. 2009; 25(11):2655-2662.
111 Messerli F, Frishman WH, Elliott WJ. Effects of verapamil and trandolapril in the treatment of hypertension. Trandolapril study group. Am J Hypertens. 1998; 11(3 Pt 1):322-327.
112 Karlberg BE, Andrup M, Oden A. Efficacy and safety of a new long-acting drug combination, trandolapril/verapamil as compared to monotherapy in primary hypertension. Swedish TARKA trialists. Blood Press. 2000; 9:140-145.
113 De Quattro V, Lee D. Fixed-dose combination therapy with trandolapril and verapamil SR is effective in primary hypertension. Trandolapril study group. Am J Hypertens. 1997; 10(7 Pt 2):138S-145S.
114 Ruilope LM, Usan L, Segura J, et al. Intervention at lower blood pressure levels to achieve target goals in type 2 diabetes: PRADID (PResion Arterial en DIabeticos tipo Dos) study. J Hypertens. 2004; 22(1):217-222.
115 Ruggenenti P, Fassi A, Ilieva AP, et al for the BENEDICT Investigators. Preventing microalbuminuria in type 2 diabetes. N Engl J Med. 2004; 351(19):1941-1951.
116 Pepine CJ, Handberg EM, Cooper-De Hoff RM, et al. A calcium antagonist vs. a non-calcium antagonist hypertension treatment strategy for patients with coronary artery disease. The International Verapamil-Trandolapril Study (INVEST): a randomized controlled trial. JAMA. 2003; 290(21):2805-2816.
117 Cooper-Dehoff R, Cohen JD, Bakris GL, et al. Predictors of development of diabetes mellitus in patients with coronary artery disease taking antihypertensive medications (findings from the International VErapamil SR-Trandolapril Study [INVEST]). Am J Cardiol. 2006; 98(7):890-894.
118 Bangalore S, Messerli FH, Cohen JD, et al. Verapamil-sustained release-based treatment strategy in equivalent to atenolol-based treatment strategy at reducing cardiovascular events in patients with prior myocardial infarction: an International VErapamil SR-Trandolapril (INVEST) substudy. Am Heart J. 2008; 156(2):241-247.

119 Lv Y, Zou Z, Chen GM, et al. Amlodipine and angiotensin-converting enzyme inhibitor combination versus amlodipine monotherapy in hypertension: a meta-analysis of randomized controlled trials. Blood Press Monit. 2010; 15(4):195-204.