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Angiotensin Converting Enzyme Inhibitors (ACEIs) and Angiotensin II Receptor Antagonists (ARBs), and Combinations Step Therapy Criteria

ARB Step therapy may be implemented as a 1-Step or 2-Step program:

1-Step edit, with generic ACEI or ARB, including combinations, before brand ARB or ARB combination OR

2-Step edit, with generic ACEI or ARB, including combinations, before *preferred* brand ARB or combination AND both generic ACEI or ARB, including combinations, and *preferred* brand ARB or combination before any *nonpreferred* brand ARB or combination

For BlueCross BlueShield of Illinois, BlueCross BlueShield of New Mexico, BlueCross BlueShield of Oklahoma, and BlueCross BlueShield of Texas, ARB step therapy will be implemented as a 1-step edit, with generic ACEI or ARB, including combinations, before brand ARB or ARB combination.

Angiotensin Converting Enzyme Inhibitors (ACEIs)		
Brand	Generic	Dosage Form
Accupril®	quinapril*	oral tablets
Accuretic®	quinapril/hydrochlorothiazide*	oral tablets
Aceon®	perindopril*	oral tablets
Altace®	ramipril*	oral tablets, oral capsules
Capoten®	captopril*	oral tablets
Capozide®	captopril/hydrochlorothiazide*	oral tablets
Lexxel®	enalapril/felodipine ER	oral tablets
Lotensin®	benazepril*	oral tablets
Lotensin® HCT	benazepril/hydrochlorothiazide*	oral tablets
Lotrel®	benazepril/amlodipine*	oral capsules
Mavik®	trandolapril*	oral tablets
Monopril®	fosinopril*	oral tablets
Monopril® HCT	fosinopril/hydrochlorothiazide*	oral tablets
Prinivil®	lisinopril*	oral tablets
Prinzide®	lisinopril/hydrochlorothiazide*	oral tablets
Tarka®	trandolapril/verapamil ER	oral tablets
Univasc®	moexipril*	oral tablets
Uniretic®	moexipril/hydrochlorothiazide*	oral tablets
Vasotec®	enalapril*	oral tablets
Vaseretic®	enalapril/hydrochlorothiazide*	oral tablets
Zestril®	lisinopril*	oral tablets
Zestoretic®	lisinopril/hydrochlorothiazide*	oral tablets

* Agent available as generic

Angiotensin II Receptor Antagonists (ARBs)		
Brand	Generic	Dosage Form
Atacand [®]	candesartan	oral tablets
Atacand HCT [®]	candesartan/hydrochlorothiazide	oral tablets
Avapro [®]	irbesartan	oral tablets
Avalide [®]	irbesartan/hydrochlorothiazide	oral tablets
Azor [®]	olmesartan/amlodipine	oral tablets
Benicar [®]	olmesartan	oral tablets
Benicar HCT [®]	olmesartan/hydrochlorothiazide	oral tablets
Cozaar [®]	losartan	oral tablets
Exforge [®]	valsartan/amlodipine	oral tablets
Exforge HCT [®]	valsartan/amlodipine/ hydrochlorothiazide	oral tablets
Hyzaar [®]	losartan/hydrochlorothiazide	oral tablets
Diovan [®]	valsartan	oral tablets
Diovan HCT [®]	valsartan/hydrochlorothiazide	oral tablets
Micardis [®]	telmisartan	oral tablets
Micardis [®] HCT	telmisartan/hydrochlorothiazide	oral tablets
Teveten [®]	eprosartan	oral tablets
Teveten [®] HCT	eprosartan/hydrochlorothiazide	oral tablets
Twynsta [®]	telmisartan/amlodipine	oral tablets
Valturna [®]	aliskiren/valsartan	oral tablets

FDA-APPROVED INDICATIONS ^{1-34,75-79,89,95,96}

The following information is taken from individual drug prescribing information and is provided here as background information only. Not all FDA-approved indications may be considered medically necessary. All criteria are found in the section "Prior Authorization Criteria for Approval."

Table 1: FDA-approved Indications of ACEIs and ACEI Combinations ^{1-20,75-77}

ACEI, ACEI Combo	Hypertension	LV systolic Heart Failure	Post-MI	Nephropathy (type 1 DM)	CV risk reduction in high risk patients
benazepril	✓				
captopril	✓	✓	✓ ^a	✓	
enalapril	✓	✓	✓ ^a		
fosinopril	✓	✓			
lisinopril	✓	✓	✓		
moexipril	✓				
perindopril	✓				✓ ^c
quinapril	✓	✓			
ramipril	✓		✓ ^b		✓ ^d
trandolapril	✓	✓			
benazepril/HCTZ	✓				
captopril/HCTZ	✓				
enalapril/HCTZ	✓				
fosinopril/HCTZ	✓				
lisinopril/HCTZ	✓				
moexipril/HCTZ	✓				
quinapril/HCTZ	✓				
benazepril/amlodipine	✓				
enalapril/felodipine	✓				
trandolapril/verapamil	✓				

LV= left ventricular; MI = myocardial infarction; DM = diabetes mellitus; CV = cardiovascular; HCTZ = hydrochlorothiazide

a - with LV dysfunction and/or heart failure

b - with heart failure

c - In patients with stable coronary artery disease (CAD) to reduce risk of CV mortality and nonfatal MI,

d - ≥55 years old at high risk of developing a major CV event because of history of CAD, stroke, peripheral vascular disease, DM

Table 2: FDA-approved Indications of ARBs and ARB Combinations 21-34,78,79,95,96

ARB, ARB Combo	Hypertension	Hypertension/LVH	Post-MI	Heart Failure	DM nephropathy
candesartan	✓			✓ ^{bde}	
eprosartan	✓				
irbesartan	✓				✓ ^c
losartan	✓	✓ ^a			✓ ^c
olmesartan	✓				
telmisartan	✓				
valsartan	✓		✓	✓ ^{bd}	
candesartan/HCTZ	✓				
eprosartan/HCTZ	✓				
irbesartan/HCTZ	✓				
losartan/HCTZ	✓	✓ ^a			
olmesartan/HCTZ	✓				
telmisartan/HCTZ	✓				
valsartan/HCTZ	✓				
olmesartan/amlodipine	✓				
telmisartan/amlodipine	✓				
valsartan/amlodipine	✓				
valsartan/amlodipine/ hydrochlorothiazide	✓				
aliskiren/valsartan	✓				

LVH = left ventricular hypertrophy; MI = myocardial infarction; DM = diabetes mellitus; ; HCTZ = hydrochlorothiazide

a - Reduction in the risk of stroke in patients with hypertension and LVH

b - Treatment of heart failure [New York Heart Association (NYHA) class II-IV] in patients who are unable to tolerate an ACEI

c - Treatment of diabetic nephropathy with an elevated serum creatinine and in patients with type 2 DM and hypertension

d - In patients intolerant of ACEIs

e - In combination with ACEI

All of the angiotensin converting enzyme inhibitor (ACEI) and angiotensin II receptor antagonist (ARB) single entity agents may be used as monotherapy or in combination for the treatment of hypertension.

RATIONALE FOR STEP THERAPY

The intent of the ACEI/ARB step therapy criteria is to promote the use of cost-effective generic products - ACEIs, ACEI combinations (ACEI/diuretics or ACEI/calcium channel blockers [CCBs]), ARBs - over the more expensive brand ACEIs or brand ACEI combinations and over brand ARBs or brand ARB combinations (ARB/diuretics, ARB/CCBs, or ARB/renin inhibitors). In addition, the 2-step option will promote the use of preferred brand ARBs or ARB combinations before the nonpreferred brand ARBs and ARB combinations.

Hypertension

All of the currently available ACEIs are indicated for the treatment of hypertension and there are minimal data to suggest that one ACEI is superior to another.^{35,36} Multiple outcome trials with ACEIs in the treatment of hypertension have been conducted. Two outcome trials, ALLHAT³⁷ and ANBP2,³⁸ are particularly important in establishing ACEIs as first or second line treatment options for hypertension.

Each of the ARBs is also indicated for the treatment of hypertension. For the ARBs, there are four major outcome trials showing benefit from their use in treatment of hypertension.³⁹⁻⁴² A two part meta-analysis evaluating all ARBs but olmesartan⁴³ showed only minor differences in antihypertensive effects with all ARBs when given at their recommended doses. This meta-analysis concluded that there is little clinically significant difference in efficacy between the six ARBs in the treatment of hypertension.⁴³ There are no outcome trials in hypertension powered to show differences in clinical endpoints between any two ACEIs or ARBs.

Three Cochrane reviews separately analyze the effects of ACEIs, ARBs, and direct renin inhibitors in primary hypertension.⁹⁰⁻⁹² The reviews report the results of analyses based on the published results of randomized clinical trials of each class of drugs versus placebo. The authors say that their systematic

reviews of ACEIs and ARBs provide the best available published evidence about the dose-related blood pressure lowering efficacy of these drugs for the treatment of primary hypertension. The authors concluded that there are no differences in blood pressure lowering ability between individual ACEIs or ARBs and, as a result, substantial cost savings could be achieved by prescribing the least expensive drug in each class. In addition, they found that 60% to 70% of the blood pressure lowering effects of ACEIs and ARBs occurred with recommended starting doses and that there was no evidence for using doses higher than half the manufacturer's maximum recommended daily dose.⁹⁰⁻⁹²

Published guidelines and systematic reviews that have evaluated ACEIs and ARBs for treatment of hypertension are summarized below [see also Chapter 5.6A: Antihypertensives: ACE Inhibitors & ACE/Diuretic Combinations and Chapter 5.6B: Antihypertensives: Angiotensin II Receptor Blockers & Combinations]:^{80, 81}

Table 3: Recommendations for ACEIs, ARBs in Treatment of Hypertension ^{44-49,71,80,81,85,93}

Guideline/ Review	Place for ACEIs	Place for ARBs	Comments
JNC-7 ⁴⁵ (2003)	May use in combination with diuretic as first-line "Compelling indications" include: HF, DM, CKD, post-MI, high coronary disease risk, recurrent stroke prevention	May use in combination with diuretic as first-line "Compelling indications" include: HF, DM, CKD	Excellent clinical trial outcome data prove that lowering blood pressure with several classes of drugs, including ACEIs and ARBs [plus others] will all reduce the complications of hypertension.
ESH/ESC ⁴⁹ (2003)	Benefits of ACEIs and ARBs have been shown in placebo-controlled trials. Both classes are suitable for initiation and maintenance of therapy. Compelling reasons for use: HF, LFD, post-MI, type 1 DM, proteinuria	Benefits of ACEIs and ARBs have been shown in placebo-controlled trials. Both classes are suitable for initiation and maintenance of therapy. Compelling reasons for use: type 2 DM, diabetic microalbuminuria, proteinuria, LVH, ACEI-induced cough	Renoprotective benefits of ACEIs have been shown in type 1 DM and of ARBs in type 2 DM Both contraindicated in hyperkalemia, bilateral renal stenosis, and pregnancy
BHS ⁴⁸ (2004)	More effective in white hypertensive patients <55 yrs	More effective in white hypertensive patients <55 yrs	
K/DOQI ⁷¹ (2004)	ACEIs and ARBs can be used safely in most patients with CKD. They should be used at moderate to high doses.	ACEIs and ARBs can be used safely in most patients with CKD. They should be used at moderate to high doses.	ACEIs and ARBs can be used in combination to lower blood pressure or reduce proteinuria.
NICE ⁴⁷ (2006)	First choice in white hypertensive patients <55 yrs	Alternate first choice if an ACEI is not tolerated	
AHA/ASA ^{80,81} (2006)	In diabetic hypertensive patients, ACEIs and ARBs are more effective in reducing the progression of renal disease and are recommended as first choice medications.	In diabetic hypertensive patients, ACEIs and ARBs are more effective in reducing the progression of renal disease and are recommended as first choice medications.	
AHRQ ⁴⁴ (2007)	ACEIs and ARBs appear to have similar long-term effects on blood pressure	ACEIs and ARBs appear to have similar long-term effects on blood pressure	ACEIs associated with greater risk of cough
AHA ⁸⁵ (2007)	ACEI appropriate to reduce blood pressure	ARB appropriate in patients intolerant of ACEIs	
ADA ⁴⁶ (2008)	Patients with DM and hypertension should take either ACEI or ARB	Patients with DM and hypertension should take either ACEI or ARB	If one of these classes (ACEI or ARB) is not tolerated the other should be substituted

Guideline/ Review	Place for ACEIs	Place for ARBs	Comments
ASH ⁹³ (2008)	ACEI appropriate for initial therapy for diabetic patients with blood pressure <20 mm Hg above goal	ARB appropriate for initial therapy for diabetic patients with blood pressure <20 mm Hg above goal	Once daily RAS blocker (ACEI or ARB) is recommended in algorithm; second agent recommended includes diuretics or CCBs

CKD = chronic kidney disease; DM = diabetes mellitus; HF = heart failure; LVD = left ventricular dysfunction; LVH = left ventricular hypertrophy; MI = myocardial infarction; RAS= renin angiotensin system
 ADA = American Diabetes Association; AHA = American Heart Association; AHRQ = Agency for Healthcare Research and Quality;
 ASH = American Society of Hypertension; BHS = British Hypertension Society; ESH/ESC = European Society of Hypertension/
 European Society of Cardiology; JNC-7 = Joint National Committee (Blood Pressure) 7th report;
 K/DOQI= Kidney Disease Outcomes Quality Initiative; NICE = National Institute for Health and Clinical Excellence;

Aliskiren 150 mg and 300 mg and valsartan 160 mg and 320 mg were studied alone and in combination in an 8-week, 1,797-patient, randomized, double-blind, placebo-controlled, parallel-group, 4-arm, dose-escalation study. The dosages of aliskiren and valsartan were started at 150 mg and 160 mg, respectively, and increased at four weeks to 300 mg and 320 mg, respectively. Seated trough blood pressure was measured at baseline, 4 weeks, and 8 weeks. Blood pressure reductions with the combinations were statistically significantly ($p < 0.05$) greater than the reductions with the monotherapies. At all levels of baseline blood pressure, the probability of achieving any given diastolic or systolic goal is greater with the combination than for either monotherapy.⁹⁵

Heart Failure, including Post-Myocardial Infarction (MI)

ACEIs are well established for the treatment of heart failure (HF), and are strongly recommended in treatment guidelines.^{47,50} A retrospective cohort study comparing the effectiveness of different ACEIs in the treatment of patients with HF found no significant differences in the combined endpoint of hospital readmission for HF or mortality and suggests a class effect among the ACEIs for this indication.⁵¹ There are outcomes data for three ARBs (candesartan, losartan, valsartan) in congestive heart failure (CHF).^{45,47,50,54-58} One head-to-head trial found no difference in mortality between an ACEI and an ARB, but due to the study design, equivalence could not be concluded.⁵⁶ In another head-to-head trial valsartan was found to be as effective as captopril in patients who were at high risk for cardiovascular events after MI.⁵⁸ ARBs may be a reasonable alternative in HF patients unable to tolerate ACEIs.

Published guidelines and systematic reviews that have evaluated ACEIs and ARBs for treatment of HF, including post-MI are summarized below [see Chapter 5.6A: Antihypertensives: ACE Inhibitors & ACE/ Diuretic Combinations and Chapter 5.6B: Antihypertensives: Angiotensin II Receptor Blockers & Combinations]:^{80, 81}

Table 4: Recommendations for ACEIs and ARBs in Treatment of Heart Failure, Post-MI

Guideline/ Review	Place for ACEIs	Place for ARBs	Comments
VA ^{81,88} [Chronic Heart Failure] (2002)	Patients with HF Stage B or C should receive an ACEI, regardless of presence of LVSD.	ARB not considered unless patient intolerant of ACEIs; ARBs not yet shown to be equivalent or superior to ACEIs in HF	Benefit of combination of ARB and ACEI is still to be determined
ESC ⁵² [Cardiovascular disease] (2004)	All HF or asymptomatic patients with LVD without contraindications should receive ACEIs	[not mentioned]	Use ACEIs with caution with significant renal dysfunction, hyperkalemia, symptomatic hypotension
ACP ^{80,81} [Chronic Stable Angina] (2004)	ACEIs should be used in patients with symptomatic chronic stable angina; they should also be used in asymptomatic patients with CAD who have diabetes or systolic dysfunction	[not mentioned]	

Guideline/ Review	Place for ACEIs	Place for ARBs	Comments
AHA/ACC ^{80,81} [Secondary Prevention, CAD] (2006)	ACEIs should be used in all patients with LVEF \leq 40% and in those with hypertension, DM, CKD	Use in patients who are intolerant of ACEIs and have HF or MI with LVEF $<$ 40%	Consider combination ACEIs and ARBs in systolic-dysfunction HF
HFSA ⁷⁴ [Heart Failure] (2006)	ACEIs are recommended for prevention of HF in patients at high risk, recommended for patients after an MI, with systolic dysfunction or preserved systolic function ACEIs are recommended for asymptomatic & symptomatic patients with LVEF $<$ 40% ACEIs should be considered in all patients with HF and preserved LVEF with symptoms or DM	ARBs are recommended for patients intolerant of ACEIs. ARBs valsartan and candesartan specifically have shown benefit ARBs may be considered as initial therapy rather than ACEIs for patients with HF post-MI or chronic HF and systolic dysfunction	Routine combination of ACEIs and ARBs is not recommended in asymptomatic patients with LVEF $<$ 40% Combination therapy with ACEI and ARB may be considered in patients with HF and systolic dysfunction remaining symptomatic on ACEI and beta blocker therapy
ACC/AHA ^{81,87} [Chronic Stable Angina] (2007)	ACEIs recommended first line for blood pressure control in patients with CAD. ACEIs should be continued indefinitely in all patients with LVEF \leq 40% and in those with hypertension, DM, CKD It is reasonable to use ACEIs among lower-risk patients with mildly reduced or normal LVEF	ARBs recommended for patients with chronic stable angina with hypertension, HF, or MI with LVEF \leq 40% and intolerant of ACEIs ARBs may be considered in combination with ACEIs for HF due to LVSD	
ACC/AHA ⁸⁶ [ST-elevation MI] (2008)	ACEIs beneficial within first 24 hours of MI with ST elevation [STEMI] or with HF or with MI and LVEF $<$ 40% or with HF Among lower risk patients (normal LVEF) recovering from STEMI use of ACEIs is reasonable	ARBs are recommended in patients who are intolerant of ACEIs and HF or have had MI with LVEF \leq 40% ARBs are beneficial in other patients who are ACEI intolerant and have hypertension	
ACC/AHA ^{50,94} [Chronic Heart Failure] (2005; 2009 update)	ACEIs should be prescribed for all patients with HF due to LVD with reduced LVEF unless there is a contraindication	ARBs are reasonable to use as alternatives to ACEIs as first line therapy The addition of an ARB may be considered in persistently symptomatic patients with reduced LVEF who are already being treated with conventional therapy	Preference may be given to ACEIs shown to reduce morbidity and mortality in clinical trials in HF or post MI (captopril, enalapril, lisinopril, ramipril, perindopril, trandolapril) The ARBs valsartan and candesartan have demonstrated benefit by reducing hospitalizations and mortality

CAD = coronary artery disease; CKD = chronic kidney disease; DM = diabetes mellitus; HF = heart failure; LVEF = left ventricular ejection fraction; LVD = left ventricular dysfunction; LVH = left ventricular hypertrophy; LVSD = left ventricular systolic dysfunction; MI = myocardial infarction; STEMI = ST-elevation myocardial infarction
ACC = American College of Cardiology; ACP = American College of Physicians; AHA = American Heart Association; ASA = American Stroke Association, ESC = European Society of Cardiology; HFSA = Heart Failure Society of America; VA = Veterans Administration

Renal Disease, Diabetic Nephropathy

While both ACEIs and ARBs given alone have been found to decrease the progression of microalbuminuria to overt proteinuria, ACEIs currently have the strongest evidence for delaying progression of chronic non-diabetic renal disease as well as nephropathy in type 1 diabetes.³⁶

Two ARBs, losartan and irbesartan, have been found to be of benefit in preventing worsening renal function in type 2 diabetes patients with proteinuria;^{41,57} no ACEIs have been proven, in a single randomized, controlled trial to offer this benefit in this population. However, captopril has been found to reduce risk of a combined endpoint of death, dialysis and transplantation in type 1 diabetes patients with overt proteinuria,⁶⁰ and a meta-analysis of patients with or without diabetes and with overt proteinuria found that ACEIs reduced risk of a composite of doubling of serum creatinine or development of end stage renal disease (ESRD).⁶¹ Furthermore, persons with type 2 diabetes and renal disease are at increased cardiovascular risk. There is evidence that indicates this risk may be reduced with the use of an ACEI. In the absence of long-term outcome trials comparing an ACEI to an ARB to determine if these agents provide similar benefits in patients with type 2 diabetes and microalbuminuria or nephropathy, major clinical guidelines either are neutral or recommend an ACEI as first line therapy.^{46,62,63}

Guidelines from the American Diabetes Association (ADA)⁶² currently state: "In the treatment of albuminuria/nephropathy both ACEIs and ARBs can be used. In patients with type 1 diabetes, with or without hypertension, with any degree of albuminuria, ACEIs have been shown to delay the progression of nephropathy. In patients with type 2 diabetes, hypertension and microalbuminuria, ACEIs and ARBs have been shown to delay the progression to macroalbuminuria. In those with type 2 diabetes, hypertension, macroalbuminuria (>300mg/day), nephropathy, or renal insufficiency, an ARB should be strongly considered. If one class is not tolerated, the other should be substituted."⁶²

Safety and Tolerability Profile

In a drug class review of ACEIs for its practitioner-managed prescription drug plan, the Oregon Evidence-based Practice Center identified 24 head-to-head trials comparing adverse event rates of different ACEIs in the treatment of hypertension, prevention of events after MI, and HF.⁶⁴ There was little evidence of meaningful differences in tolerability profiles for the agents.⁶⁴ As a class, ARBs are also well tolerated, with adverse events profiles for the agents generally similar to placebo,^{64,65} though large placebo-controlled trials have found more discontinuations due to adverse events with ARBs.^{54,66} Some trials comparing ACEIs and ARBs have found differences in rate of cough, and in discontinuations due to adverse events, favoring the ARBs, primarily due to differences in rate of cough.^{55,56,67,68} Although the rate of angioedema appears to be lower with ARBs than ACEIs, the rates are low for each class.⁶⁸ It is unclear if there are important differences in effects on potassium between ACEIs and ARBs.

Conclusions

Although the strongest evidence supporting the use of ACEIs in CHF, hypertension, and MI have involved three specific agents; enalapril, lisinopril, and captopril, the findings are often extrapolated to other ACEIs, and a class effect is often presumed despite differences in pharmacokinetic and pharmacodynamic properties among agents. There have been no published head-to-head trials comparing the effectiveness of the different ACEIs.^{69,70}

Lisinopril, enalapril and captopril have the most outcome data of the class of ACEIs. However, seven sets of clinical guidelines (JNC 7⁴⁵, European Society of Cardiology/European Society of Hypertension⁴⁹, AHA/ACC⁶⁰, British Hypertension Society⁴⁸, National Kidney Foundation⁷¹, American Diabetes Association⁴⁶, Agency for Healthcare Research and Quality [AHRQ]⁴⁴) consider all drugs in this class equal in the treatment of each of the FDA approved indications.

ACEIs are first line treatment for hypertension, HF, and for renal protection in patients with and without diabetes. ARBs should be used only after a patient has become intolerant to the ACEI due to cough or angioedema.⁷²⁻⁷⁴ Available evidence and current guidelines do not suggest ARBs have a preferred role over ACEIs in these conditions. When inhibition of the renin-angiotensin system is indicated, ACEIs or ACEI/ diuretics should generally be preferred over ARBs; ARB use should be limited to patients with a documented failure, allergy, contraindication, or intolerance to an ACEI.

The 2006 Oregon Health Resources Commission Subcommittee Report titled “Angiotensin II Receptor Antagonists (AIIRA)”⁶⁵ states that in patients with essential hypertension, high cardiovascular risk factors, recent MI, HF or nephropathy there are no data to suggest that one ARB is superior to another for efficacy and safety. Additionally, there is inadequate data to determine whether there is a difference between the ARBs with respect to demographics (age, racial groups, or sex), in combination with other medications, or in hypertensive patients with other comorbidities.⁶⁵

ELECTRONIC EDITS

The overall process for step therapy requires that another drug or drugs be tried in a specific previous time period before the claim drug. The intent of the initial step therapy edit is to electronically identify patients and automatically pay for drug claims for brand ACEIs, brand ACEI combinations, brand ARBs, or brand ARB combinations when prerequisites are found or when there is a prior medication history for that specific drug. Approval of these agents if previous use is identified assures no disruption of therapy for those patients already stabilized on the medication. The 90-day search period was chosen to capture the most current therapy. If the patient has met any of the requirements outlined below, the requested step therapy medication will be paid under the patient’s current prescription benefit.

Table 5: Summary of Brand ACEI or ACEI Combinations Step Therapy

Targeted Agent(s)	All brand ACEI and ACEI combination (diuretic or CCB) products
Is auto-grandfathering implemented? (with look-back time frame)	Y (90 days ^a)
Prerequisite Agent(s)	NA – auto-grandfathering only
Number of prerequisites required	NA
Prerequisite look-back time frame	NA
Age-related edit?	NA
Additional comments	Any ACEI or ACEI combination product will auto-grandfather another product with the same ACEI.

a - The system searches for a claim with a days supply that begins or ends in the past 90 days. For claims with a 30-day supply the system would be able to identify a claim processed for payment between 1 and 120 days prior to the new claim. For claims that are dispensed as an extended days supply (90 days), the system would identify a claim processed between 1 and 180 days.

Table 6: Details of Brand ACEI or ACEI Combinations Step Edit

Targeted Agents	GPIs	Prior Agents	GPIs	Look-back Time frames
Accupril, Aceon, Altace, Capoten, Lotensin, Mavik, Monopril, Prinivil, Univasc, Vasotec, Zestril	3610*****, multisource code M, N, or O	For Auto-grandfathering, ANY ONE of: Accupril, Aceon, Altace, Capoten, Lotensin, Mavik, Monopril, Prinivil, Univasc, Vasotec, Zestril, Accuretic, Capozide,	3610*****, 36991502*****, 36991802*****, multisource code M, N, or O, set up at drug or GPI 10 level	Auto-grandfathering look-back time frame: 90 days ^a
Accuretic, Capozide, Lotensin HCT, Monopril HCT, Prinzide, Uniretic, Vaseretic, Zestoretic	369918*****, multisource code M, N, or O	Lotensin HCT, Monopril HCT, Prinzide, Uniretic, Vaseretic, Zestoretic, Lexxel, Lotrel, Tarka	**single entity and combination (diuretic or CCB) with same ACEI will auto-grandfather each other	
Lexxel, Lotrel, Tarka	369915*****, multisource code M, N, or O			

a - The system searches for a claim with a days supply that begins or ends in the past 90 days. For claims with a 30-day supply the system would be able to identify a claim processed for payment between 1 and 120 days prior to the new claim. For claims that are dispensed as an extended days supply (90 days), the system would identify a claim processed between 1 and 180 days.

Table 7: Summary of Brand ARB and ARB Combination Step Therapy

	1-Step Option	2-Step Option-Preferred Brand	2-Step Option-Nonpreferred Brand
Targeted Agent(s)	All brand ARB and ARB combination (diuretic, CCB, or renin inhibitor) products	All preferred brand ARB and ARB combination (diuretic, CCB, or renin inhibitor) products - determined by client	All nonpreferred brand ARB and ARB combination (diuretic, CCB, or renin inhibitor) products - determined by client
Is auto-grandfathering implemented? (with look-back time frame)	Y (90 days ^a)	Y (90 days ^a)	Y (90 days ^a)
Prerequisite Agent(s)	any generic ACEI or ACEI combination (diuretic or CCB) or any generic ARB/ARB combination (as available)	any generic ACEI, ACEI combination or any generic ARB or ARB combination (as available)	any generic ACEI, ACEI combination or any generic ARB or ARB combination (as available) AND a preferred brand ARB
Number of prerequisites required	1	1	2
Prerequisite look-back time frame	90 days ^a	90 days ^a	180 days ^b
Age-related edit?	NA	NA	NA
Additional comments	A brand ARB or ARB combination product will auto-grandfather another product with the same ARB.	A brand ARB or ARB combination product will auto-grandfather another product with the same ARB.	A brand ARB or ARB combination product will auto-grandfather another product with the same ARB.

a - The system searches for a claim with a days supply that begins or ends in the past 90 days. For claims with a 30-day supply the system would be able to identify a claim processed for payment between 1 and 120 days prior to the new claim. For claims that are dispensed as an extended days supply (90 days), the system would identify a claim processed between 1 and 180 days.

b - The system searches for a claim with a days supply that begins or ends in the past 180 days. For claims with a 30-day supply the system would be able to identify a claim processed for payment between 1 and 210 days prior to the new claim. For claims that are dispensed as an extended days supply (90 days), the system would identify a claim processed between 1 and 270 days.

Table 8: Details of Brand ARB and ARB Combination Step Therapy - 1-Step Edit

Targeted Agents	GPIs	Prior Agents	GPIs	Look-back Time frames
Atacand, Avapro, Benicar, Cozaar, Diovan, Micardis, Teveten, Atacand HCT, Avalide, Benicar HCT, Hyzaar, Diovan HCT, Micardis HCT, Teveten HCT, Azor, Exforge, Twynsta, Exforge HCT, Valtorna	3615***** 369930***** 369940***** 369945***** 369965***** multisource code M, N, or O	For Prerequisites, ANY ONE of: benazepril, benazepril/HCTZ, benazepril/amlodipine, captopril, captopril/HCTZ, enalapril, enalapril/HCTZ, fosinopril, fosinopril/HCTZ, lisinopril, lisinopril/HCTZ, moexipril, moexipril/HCTZ, perindopril, ramipril, quinapril, quinapril/HCTZ, trandolapril OR any generic ARB product, as available	3610***** 369915***** 369918***** multisource code Y OR 3615***** 369930***** 369940***** 369945***** 369965***** multisource code Y	Prerequisite look-back time frame: 90 days ^a

a - The system searches for a claim with a days supply that begins or ends in the past 90 days. For claims with a 30-day supply the system would be able to identify a claim processed for payment between 1 and 120 days prior to the new claim. For claims that are dispensed as an extended days supply (90 days), the system would identify a claim processed between 1 and 180 days.

Table 8: Details of Brand ARB and ARB Combination Step Therapy - 1-Step Edit (cont.)

Targeted Agents	GPIs	Prior Agents	GPIs	Look-back Time frames
Atacand, Avapro, Benicar, Cozaar, Diovan, Micardis, Teveten, Atacand HCT, Avalide, Benicar HCT, Hyzaar, Diovan HCT, Micardis HCT, Teveten HCT, Azor, Exforge, Twynsta, Exforge HCT, Valturna	3615***** 369930***** 369940***** 369945***** 369965***** multisource code M, N, or O	For Auto-grandfathering, ANY ONE of: Atacand, Avapro, Benicar, Cozaar, Diovan, Micardis, Teveten, Atacand HCT, Avalide, Benicar HCT, Hyzaar, Diovan HCT, Micardis HCT, Teveten HCT, Azor, Exforge, Twynsta, Exforge HCT, Valturna	3615***** 369930***** 369940***** 369945***** 369965***** multisource code M, N, or O, set up at drug or GPI 10 level **single entity and combination (diuretic, CCB, or renin inhibitor) with same ARB will auto-grandfather each other	Auto-grandfathering look-back time frame: 90 days ^a

a - The system searches for a claim with a days supply that begins or ends in the past 90 days. For claims with a 30-day supply the system would be able to identify a claim processed for payment between 1 and 120 days prior to the new claim. For claims that are dispensed as an extended days supply (90 days), the system would identify a claim processed between 1 and 180 days.

Table 9: Details of Brand ARB and ARB Combination Step Therapy - 2-Step Edit

Targeted Agents	GPIs	Prior Agents	GPIs	Look-back Time frames
<i>Preferred brand ARBs and ARB combinations</i>	Determined by client - 3615***** 369930***** 369940***** 369945***** 369965***** multisource code M, N, or O set up at drug or GPI 10 level	For Prerequisites, ANY ONE of: Generic ACEI or ACEI combination [listed under 1-step] OR any generic ARB product, as available	3610***** 369915***** 369918***** multisource code Y OR 3615***** 369930***** 369940***** 369945***** 369965***** multisource code Y	Prerequisite look-back time frame: 90 days ^a
		For Auto-grandfathering, ANY ONE of: Preferred Brand ARB or ARB combination, determined by client	3615***** 369930***** 369940***** 369945***** 369965***** multisource code M, N, or O, set up at drug or GPI 10 level **single entity and combination (diuretic CCB, renin inhibitor) with same ARB will auto-grandfather each other	Auto-grandfathering look-back time frame: 90 days ^a

a - The system searches for a claim with a days supply that begins or ends in the past 90 days. For claims with a 30-day supply the system would be able to identify a claim processed for payment between 1 and 120 days prior to the new claim. For claims that are dispensed as an extended days supply (90 days), the system would identify a claim processed between 1 and 180 days.

Table 9: Details of Brand ARB and ARB Combination Step Therapy - 2-Step Edit (cont.)

Targeted Agents	GPIs	Prior Agents	GPIs	Look-back Time frames
Nonpreferred brand ARBs and ARB combinations	Determined by client - 3615***** 369930***** 369940***** 369945***** 369965***** multisource code M, N, or O set up at drug or GPI 10 level	<p>For Prerequisites, ANY ONE of: Generic ACEI or ACEI combination [listed under 1-step] OR any generic ARB product, as available</p> <p>AND ANY ONE of: Preferred Brand ARB or ARB combination, determined by client</p>	<p>3610***** 369915***** 369918***** multisource code Y</p> <p>OR</p> <p>3615***** 369930***** 369940***** 369945***** 369965***** multisource code Y</p> <p>AND Determined by client 3615***** 369930***** 369940***** 369945***** 369965***** multisource code M, N, or O set up at drug or GPI 10 level</p>	<p>Prerequisite look-back time frame:</p> <p>180 days^b</p>
		<p>For Auto-grandfathering, ANY ONE of: Nonpreferred brand ARB or ARB combination, determined by client</p>	<p>3615***** 369930***** 369940***** 369945***** 369965***** multisource code M, N, or O, set up at drug or GPI 10 level</p> <p>**single entity and combination (diuretic CCB, renin inhibitor) with same ARB will auto-grandfather each other</p>	<p>Auto-grandfathering look-back time frame:</p> <p>90 days^a</p>

a - The system searches for a claim with a days supply that begins or ends in the past 90 days. For claims with a 30-day supply the system would be able to identify a claim processed for payment between 1 and 120 days prior to the new claim. For claims that are dispensed as an extended days supply (90 days), the system would identify a claim processed between 1 and 180 days.

b - The system searches for a claim with a days supply that begins or ends in the past 180 days. For claims with a 30-day supply the system would be able to identify a claim processed for payment between 1 and 210 days prior to the new claim. For claims that are dispensed as an extended days supply (90 days), the system would identify a claim processed between 1 and 270 days.

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL

The intent of the prior authorization criteria is to provide a manual review process for claims that do not meet the electronic edit criteria and are not automatically paid. The criteria for approval through the PA process are identical to those set up in the electronic edit. Claims for a brand name ACEI will be paid if the patient used that brand name ACEI or that brand name ACEI combination within the past 90 days. In the 1-step option, claims for brand ARBs or brand ARB combinations will be approved if there is a history

of recent use of the identical ARB or if the patient has tried a generic ACEI or generic ARB product and discontinued due to failure, allergy, contraindication, or intolerance to the agent within the past 90 days. In the 2-step option, claims for preferred brand ARBs and ARB combinations will be approved if there is a history of recent use of the identical ARB or if the patient has tried a generic ACEI or generic ARB product and discontinued due to failure, allergy, contraindication, or intolerance to the agent; claims for nonpreferred brand ARBs and ARB combinations will require both a generic ACEI or generic ARB product and a preferred brand ARB or ARB combination within the past 180 days prior to approval. As in the other options, patients stabilized on a nonpreferred brand ARB will be allowed to continue on that same ARB.

Step Therapy PA Criteria for Approval

Brand ACEIs and ACEI combinations

Initial and Renewal Evaluation

1. Is the request for a brand ACEI or brand ACEI combination?
If yes, continue to 2. If no, continue to initial evaluation for ARBs.
2. Is the patient currently being treated with and stable on the requested brand ACEI or brand ACEI combination?
If yes, approve for 12 months. If no, deny.

Brand ARBs and ARB combinations – 1 Step Option

Initial and Renewal Evaluation

1. Is the request for a brand ARB or ARB combination?
If yes, continue to 2. If no, see appropriate criteria.
2. Is the patient currently being treated with and stable on the requested brand ARB or ARB combination?
If yes, approve for 12 months. If no, continue to 3.
3. Has the patient previously tried and failed therapy with a generic ACEI or generic ARB product?
If yes, approve for 12 months. If no, continue to 4.
4. Does the patient have an allergy, contraindication, or intolerance to an ACEI or ACEI combination or generic ARB product?
If yes, approve for 12 months. If no, deny.

Brand ARBs and ARB combinations – 2 Step Option

Preferred ARBs and ARB combinations

Initial and Renewal Evaluation

1. Is the request for a *preferred* brand ARB or ARB combination?
If yes, continue to 2. If no, see appropriate criteria.
2. Is the patient currently being treated with and stable on the requested *preferred* brand ARB or ARB combination?
If yes, approve for 12 months. If no, continue to 3.
3. Has the patient previously tried and failed therapy with a generic ACEI or generic ARB product?
If yes, approve for 12 months. If no, continue to 4.
4. Does the patient have an allergy, contraindication, or intolerance to an ACEI or ACEI combination or generic ARB product?
If yes, approve for 12 months. If no, deny.

Brand ARBs and ARB combinations – 2 Step Option

NONpreferred ARBs and ARB combinations

Initial and Renewal Evaluation

1. Is the request for a *nonpreferred* brand ARB or ARB combination?
If yes, continue to 2. If no, see appropriate criteria for preferred ARB or ARB combination.
2. Is the patient currently being treated with and stable on the requested *nonpreferred* brand ARB or ARB combination?
If yes, approve for 12 months. If no, continue to 3.
3. Has the patient previously tried and failed therapy with a generic ACEI or generic ARB product?
If yes, continue to 5. If no, continue to 4.
4. Does the patient have an allergy, contraindication, or intolerance to an ACEI or ACEI combination or generic ARB product?
If yes, continue to 5. If no, deny.
5. Has the patient previously tried and failed therapy with a *preferred* brand ARB or ARB combination?
If yes, approve for 12 months. If no, continue to 6.
6. Does the patient have a contraindication, allergy, or intolerance to the available *preferred* brand ARB or ARB combination?
If yes, approve for 12 months. If no, deny.

SUMMARY

Step therapy electronic edits are designed to identify specific criteria in a patient's medication history and allow payment of claims that meet the criteria. Any brand name ACEI, ACEI combination, ARB, or ARB combination is automatically paid if the patient's medication history contains at least one claim for that same brand name ACEI or ARB in the previous 90 days. For the 1-step option, a brand ARB or ARB combination will automatically pay if the patient's medication history contains at least one claim for a generic ACEI or ACEI combination or generic ARB (as available) in the previous 90 days. In the 2-step option, a *preferred* brand ARB or ARB combination is also automatically paid if the patient's medication history contains at least one claim for a generic ACEI or generic ARB product in the previous 90 days. A *nonpreferred* brand ARB or ARB combination is automatically paid if the patient's medication history contains at least one claim for a generic ACEI or generic ARB product AND at least one claim for a preferred brand ARB or ARB combination in the previous 180 days. If the patient's claims history does not contain the information specified in the edit, the prior authorization (PA) manual review process provides a member-specific review where practitioner provided patient-specific parameters are taken into consideration when reviewed.

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