

Medical Policy



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Title: Angiotensin Converting Enzyme Inhibitors and Angiotensin II Receptor Antagonists Prior Authorization Criteria

Professional

Original Effective Date: January 1, 2008

Revision Date(s):

Current Effective Date: January 1, 2008

Institutional

Original Effective Date: January 1, 2008

Revision Date(s):

Current Effective Date: January 1, 2008

Prior Authorization Form:

http://www.bcbsks.com/Customerservice/Forms/pdf/PriorAuth_ACEI-ARB-SSRI-SNRI.pdf

DESCRIPTION

Angiotensin Converting Enzyme Inhibitors		
Brand	generic	Dosage Form
Accupril®	quinapril*	oral tablets
Accuretic®	quinapril/hydrochlorothiazide*	oral tablets
Aceon®	perindopril	oral tablets
Altace®	ramipril	oral tablets
Capoten®	captopril*	oral tablets
Capozide®	captopril/hydrochlorothiazide*	oral tablets
Lotensin®	benazepril*	oral tablets
Lotensin® HCT	benazepril/hydrochlorothiazide*	oral tablets
Mavik®	trandolapril*	oral tablets
Monopril®	fosinopril*	oral tablets
Monopril® HCT	fosinopril/hydrochlorothiazide*	oral tablets
Prinivil®	lisinopril*	oral tablets
Prinzide®	lisinopril/hydrochlorothiazide*	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		
Atacand®	candesartan	oral tablets
Atacand HCT®	candesartan/hydrochlorothiazide	oral tablets
Avapro®	irbesartan	oral tablets
Avalide®	irbesartan/hydrochlorothiazide	oral tablets
Benicar®	olmesartan	oral tablets
Benicar HCT™	olmesartan/hydrochlorothiazide	oral tablets
Cozaar®	losartan	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

FDA-APPROVED INDICATIONS¹⁻³⁴

Indications for the individual agents are summarized below:

Angiotensin Converting Enzyme Inhibitors¹⁻²⁰

benazepril:	Hypertension
captopril	Hypertension, heart failure, left ventricular dysfunction after myocardial infarction (MI), nephropathy in type I diabetes
enalapril:	Hypertension, heart failure, asymptomatic left ventricular dysfunction after MI
fosinopril:	Hypertension, heart failure
lisinopril:	Hypertension, heart failure, acute myocardial infarction (within 24 hours, to improve survival)
moexipril:	Hypertension
perindopril:	Hypertension, stable coronary artery disease to reduce the risk of cardiovascular mortality or nonfatal MI
quinapril:	Hypertension, heart failure
ramipril:	Hypertension, heart failure post myocardial infarction, reduction of risk of myocardial infarction, stroke and death from cardiovascular causes in high risk patients
trandolapril:	Hypertension, heart failure or left ventricular dysfunction post myocardial infarction

All of the angiotensin converting enzyme inhibitors (ACEIs) are indicated for the treatment of hypertension. They may be used alone or in combination with other antihypertensive medications such as hydrochlorothiazide. Other indications that have received FDA approval include:

- Heart failure - captopril, enalapril, fosinopril, lisinopril, and quinapril;
- Left ventricular dysfunction or heart failure post-MI - captopril, enalapril, ramipril, and trandolapril;
- Nephropathy in type I diabetes - captopril;
- Acute MI, to improve survival - lisinopril.
- Stable coronary artery disease to reduce the risk of cardiovascular mortality or nonfatal MI - perindopril

- Reduction of the risk of myocardial infarction, stroke, and death from cardiovascular causes in high-risk patients - ramipril

*Angiotensin II Receptor Antagonists*²¹⁻³⁴

Candesartan	Hypertension, heart failure
eprosartan:	Hypertension
irbesartan:	Hypertension, nephropathy in type 2 diabetic patients
losartan:	Hypertension, nephropathy in type 2 diabetic patients, hypertensive patients with left ventricular hypertrophy
olmesartan:	Hypertension
telmisartan:	Hypertension
valsartan:	Hypertension, heart failure, post-myocardial infarction

All of the angiotensin II receptor antagonists alone and in combination with hydrochlorothiazide are indicated for the treatment of hypertension. In addition:

- Avapro (irbesartan) and Cozaar (losartan) are indicated for the treatment of diabetic nephropathy with an elevated serum creatinine and proteinuria (> 300 mg/day) in patients with type 2 diabetes and hypertension. In this population, Avapro and Cozaar reduce the rate of progression of nephropathy as measured by the occurrence of doubling serum creatinine or end-stage renal disease (need for dialysis or renal transplantation).
- Cozaar is indicated to reduce the risk of stroke in patients with hypertension and left ventricular hypertrophy, but there is evidence that this benefit does not apply to black patients.
- Diovan (valsartan) is indicated for the treatment of heart failure (NYHA class II-IV). In a controlled clinical trial, Diovan significantly reduced hospitalizations for heart failure. There is no evidence that Diovan provides added benefits when it is used with an adequate dose of an ACEI.
- Atacand has been approved for the treatment of heart failure (NYHF class II-IV and ejection fraction \leq 40%) to reduce the risk of death from cardiovascular causes and reduce hospitalizations from heart failure. Atacand has an added effect on these outcomes when used with an ACEI agent.

POLICY

RATIONALE FOR SELECTING ACEIS AND ARBS FOR PRIOR AUTHORIZATION

The intent of the ACEI/ARB prior authorization criteria is to promote the use of cost-effective generic angiotensin converting enzyme inhibitors (ACEIs) or generic ACEI/diuretic combinations over the more expensive brand ACEIs or brand ACEI/diuretic combinations and over angiotensin II receptor antagonists (ARBs) or ARB/diuretic 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} In direct comparison studies, when differences have been noted, these were considered a result

of the comparison of non-equipotent dosages or of relative reduction in blood pressure that were statistically, but not clinically significant.³⁵ 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 ACE inhibitors as first or second line treatment options for hypertension. There are no outcome trials in hypertension powered to show differences in clinical endpoints between any two ACEIs or ARBs.

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 In a two part meta-analysis evaluating all ARBs but olmesartan,⁴³ the second part analyzed 51 publications of randomized controlled clinical trials conducted with ARBs. Of these, 25 were comparative trials of ARBs versus other anti-hypertensive classes. This comprehensive analysis showed only minor differences in anti-hypertensive effects with all the ARBs when given at their recommended doses. This meta-analysis concluded that there is little clinically significant difference in efficacy between the 6 ARBs in the treatment of hypertension.⁴³

The Agency for Healthcare Research and Quality (AHRQ)⁴⁴ conducted a comparative effectiveness review of the long-term benefits and harms of ACEIs versus ARBs, focusing on their use in treating essential hypertension in adults. Forty nine studies were reviewed and evaluated, with a total of 16,347 patients followed for periods from 12 weeks to 3.3 years. The study concluded:

- ACEIs and ARBs appear to have similar long-term effects on blood pressure among individuals with essential hypertension.
- There were no consistent differential effects of ACEIs versus ARBs on several potentially important clinical outcomes including lipid levels, progression to type 2 diabetes mellitus, markers of carbohydrate metabolism/diabetes control, left ventricular mass or function, progression of renal disease.
- Due to insufficient numbers of deaths or major cardiovascular events in the included studies, it is not possible to discern any differential effect of ACEIs versus ARBs for these critical outcomes
- ACEIs have been consistently shown to be associated with greater risk of cough than ARBs.
- No differences were found in measures of general quality of life.

The most recent guidelines for treatment of hypertension in the United States (Seventh Report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure, or JNC 7)⁴⁵ concludes that:

- Excellent clinical trial outcome data prove that lowering blood pressure with several classes of drugs, including angiotensin converting enzyme inhibitors, angiotensin-receptor blockers, β -blockers, calcium channel blockers, and thiazide-type diuretics, will all reduce the complications of hypertension.
- Thiazide-type diuretics should be used as initial therapy for most patients with hypertension, either alone or in combination with 1 of the other classes (ACEIs, ARBs, β -blockers, calcium channel blockers).

These guidelines also provide a list of “compelling indications,” which are comorbid states that might influence selection of a drug for anti-hypertensive therapy; the ACEIs have more compelling indications than the ARBs. The guidelines for hypertension note that heart failure, diabetes, and chronic kidney disease are compelling indications for ARBs. Each of these, as well as post-myocardial infarction, high coronary disease risk, and recurrent stroke prevention are compelling indications for ACEIs.⁴⁵

Guidelines from the American Diabetes Association (ADA)⁴⁶ recommend either ACEIs or ARBs: Initial drug therapy may be with any drug class currently indicated for the treatment of hypertension. However, some drug classes (ACE inhibitors, β -blockers, and diuretics) have been repeatedly shown to be particularly beneficial in reducing CVD events during the treatment of uncomplicated hypertension and are therefore preferred agents for initial therapy. If ACE inhibitors are not tolerated, ARBs may be used. Additional drugs may be chosen from these classes or another drug class.⁴⁶

The 2006 guidelines from the National Institute for Health and Clinical Excellence (NICE) recommend that “In hypertensive patients younger than 55, the first choice for initial therapy should be an ACE inhibitor (or an ARB if an ACEI is not tolerated).”⁴⁷ The guidelines from the British Hypertension Society also conclude that ACEIs and ARBs may be more effective as initial blood pressure lowering treatment in younger white patients.⁴⁸ The European Society of Hypertension/European Society of Cardiology (ESH/ESC) Hypertension Guidelines recommend ACEIs and ARBs as medications whose benefits have been shown in placebo-controlled trials.⁴⁹ None of these guidelines differentiates among the ACEIs or the ARBs.

Heart Failure, including Post-Myocardial Infarction

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 generic agents available that have been shown to reduce major cardiovascular events in patients with coronary artery disease and generic agents that have shown reduction of morbidity and mortality in heart failure.³⁶

The Task Force on ACE inhibitors of the European Society of Cardiology published a consensus document on ACE inhibitors in cardiovascular disease.⁵² It recommends that all HF or asymptomatic patients with left ventricular dysfunction without contraindications should be treated with ACEIs. ACEIs remain the first choice for treatment in patients with HF. ACEIs should be used with caution in patients with significant renal dysfunction, hyperkalemia, or symptomatic hypotension.⁵²

The North of England Evidence-based Guidelines Development Project evaluated prophylaxis in patients who have experienced an MI.⁵³ They found that in unselected patients with prior MI, ACEIs are associated with a small reduction in mortality in short-

term use immediately after acute MI and a moderate reduction in mortality if used for longer term; in patients with prior MI and HF, long-term treatment with ACEIs is associated with a substantial reduction in all cause mortality as well as the incidence of nonfatal MI; and in patients with HF but not necessarily prior MI, long term treatment with ACEIs is associated with a substantial reduction in all cause mortality.⁵³

There are outcomes data for three ARBs (candesartan, losartan, valsartan) in 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 myocardial infarction.⁵⁸ ARBs may be a reasonable alternative in HF patients unable to tolerate ACEIs.

The most recent American College of Cardiology/American Heart Association 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult recommends the following:⁵⁹

- ACEIs should be prescribed for all patients with HF due to left ventricular (LV) systolic dysfunction with reduced left ventricular ejection fraction (LVEF) unless they have a contraindication to their use or have been shown to be unable to tolerate with these drugs.
- In selecting among ACEIs, it is recommended that preference be given to ACEIs that have been shown to reduce morbidity and mortality in clinical trials in HF or post MI patients (captopril, enalapril, lisinopril, perindopril, ramipril, andtrandolapril), because these studies clearly defined a dose that is effective in modifying the natural history of the disease.
- ARBs are reasonable to use as alternatives to ACEIs as first line therapy for patients with mild to moderate HF and reduced LVEF, especially for patients already taking ARBs for other indications.
- The addition of an ARB may be considered in persistently symptomatic patients with reduced LVEF who are already being treated with conventional therapy.
- For patients unable to tolerate ACEIs because of cough or angioedema, the ARBs valsartan and candesartan have demonstrated benefit by reducing hospitalizations and mortality.

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 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.^{46,62,63}

Guidelines from the American Diabetes Association (ADA)⁶² currently state: "In the treatment of albuminuria/nephropathy both ACE inhibitors and ARBs can be used. In patients with type 1 diabetes, with or without hypertension, with any degree of albuminuria, ACE inhibitors have been shown to delay the progression of nephropathy. In patients with type 2 diabetes, hypertension and microalbuminuria, ACE inhibitors 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 heart failure.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 ACE inhibitors in CHF, hypertension, and MI have involved 3 specific agents; enalapril, lisinopril, and captopril, the findings are often extrapolated to other ACE inhibitors, 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 ACE inhibitors.^{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 the treatment of hypertension, heart failure, or nephropathy. 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 Claims Edit

The intent of the initial electronic claims edit is to identify patients and automatically pay for drug claims for brand ACEIs, brand ACEI/diuretics, ARBs, or ARB/diuretics if there is a prior medication history for the 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.

For patients initiating therapy with an ACEI, this program requires use of a generic ACE or generic ACEI/diuretic. Eight of the ten ACEIs are available as generic agents and there is a generic approved for all but one of the indications for the ACEIs.

For patients initiating therapy with an ARB or ARB/diuretic, the electronic claims edit will automatically pay if the patient has a medication history of a generic ACEI or generic ACEI/diuretic in the previous 365 days. ARBs are not preferred over ACEIs but ARBs are an alternative for patients who have had a documented failure, allergy, contraindication, or intolerance to ACEIs.

Prior Authorization (PA) 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/diuretic within the past 90 days. Claims for ARBs or ARB/diuretic combinations will be approved if there is a history of use or if the patient has tried and failed a generic ACEI. The target drug will also be approved when the patient is allergic to, or intolerant of, generic agents or if the patient has

contraindications to the ACEIs that are available as generics or if the patient is currently taking the target brand and is stabilized on therapy.

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL

Initial and Renewal Evaluation for ACEI

1. Is the request for a brand ACEI or brand ACEI/diuretic combination?
If yes, continue to 2. If no, continue to evaluation for ARBs.
2. Is the patient currently being treated with the requested brand ACEI or brand ACEI/diuretic combination?
If yes, approve indefinitely. If no, deny.

Initial and Renewal Evaluation for ARBs

1. Is the request for an ARB or ARB/diuretic combination?
If yes, continue to 2. If no, see appropriate ACEI criteria.
2. Is the patient currently being treated with the requested ARB or ARB/diuretic combination?
If yes, approve indefinitely. If no, continue to 3.
3. Has the patient previously tried and failed therapy with a generic ACEI or generic ACEI/diuretic within the previous 365 days?
If yes, approve indefinitely. If no, continue to 4.
4. Does the patient have an allergy, contraindication, intolerance to an ACEI or ACEI/diuretic?
If yes, approve indefinitely. If no, deny.

CLINICAL RATIONALE FOR ELECTRONIC CLAIMS EDIT FUNCTIONS

Electronic Claims Edit

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For patients initiating therapy with an ACEI, this program requires use of a generic ACEI or generic ACEI/diuretic. Eight of the ten ACEIs are available as generic agents and there is a generic approved for all but one of the indications for the ACEIs.

For patients initiating therapy with an ARB or ARB/diuretic, the electronic claims edit will automatically pay if the patient has a medication history of a generic ACEI or generic ACEI/diuretic in the previous 365 days. ARBs are not preferred over ACEIs but ARBs are an alternative for patients who have had a documented failure, allergy, contraindication, or intolerance to ACEIs.

Prior Authorization (PA) 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/diuretic within the past 90 days. Claims for ARBs or ARB/diuretic combinations will be approved if there is a history of use or if the patient has tried and failed a generic ACEI. The target drug will also be approved when the patient is allergic to, or intolerant of, generic agents; if the patient has contraindications to the ACEIs that are available as generics; if the patient is currently taking the target brand and is stabilized on therapy.

CONCLUSION

Electronic claims edits are designed to identify specific criteria in a patient's medication history and allow payment of claims that meet the criteria. For instance, a brand name ACEI is automatically paid if the patient's medication history contains at least one claim for that brand name ACEI. If the patient's medication history does not contain the information specified in the edit the prior authorization criteria for the drug claim is applied as a member-specific review process. In this review, the prescribing physician provides patient-specific information to be taken into consideration by the reviewing physician.

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