



CIGNA HEALTHCARE COVERAGE POSITION

Subject Angiotensin Receptor Blocker Therapy

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Table of Contents

Coverage Position..... 1
General Background 2
Coding/Billing Information 5
References..... 6

Hyperlink to Related Coverage Positions

INSTRUCTIONS FOR USE

Coverage Positions are intended to supplement certain **standard** CIGNA HealthCare benefit plans. Please note, the terms of a participant's particular benefit plan document [Group Service Agreement (GSA), Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Positions are based. For example, a participant's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Position. In the event of a conflict, a participant's benefit plan document **always supercedes** the information in the Coverage Positions. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable group benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Positions and; 4) the specific facts of the particular situation. Coverage Positions relate exclusively to the administration of health benefit plans. Coverage Positions are not recommendations for treatment and should never be used as treatment guidelines. Proprietary information of CIGNA. Copyright ©2008 CIGNA

Coverage Position

CIGNA HealthCare covers Angiotensin Receptor Blocker (ARB) Therapy as medically necessary when EITHER of the following criteria is met:

- Depending upon individual client benefit plan selection, criteria requirements may consist of **ANY** of the following benefit plan options:
 - **Option 1-Generic ACE Inhibitor First**
 - failure, contraindication, or intolerance to ONE generic ACE Inhibitor
 - **Option 2- Generic ACE Inhibitor or Preferred ARB First**
 - failure, contraindication, or intolerance to ONE of the following: generic ACE Inhibitor **OR** ONE preferred ARB [i.e: Losartan (Cozaar/Hyzaar), Valsartan (Diovan/Diovan HCT)]
 - **Option 3- Dual Requirement of a Generic ACE Inhibitor First and then a Preferred ARB**
 - failure, contraindication, or intolerance to ONE generic ACE Inhibitor **AND** failure, contraindication, or intolerance to ONE preferred ARB [i.e: Losartan (Cozaar/Hyzaar), Valsartan (Diovan/Diovan HCT)]

- Patients diagnosed with **ANY** of the following indications **AND** have a history of positive clinical response to ARBs **OR** ARBs combination therapies:
 - Chronic Kidney Disease
 - Coexisting diabetes and hypertension

Angiotensin Receptor Blocker (ARB) Therapy includes the following drugs:

- Losartan / HCT(Cozaar® / Hyzaar®) – Formulary / Preferred Brand
- Valsartan / HCT(Diovan® /HCT) – Formulary / Preferred Brand
- Candesartan /HCT (Atacand® /HCT) – Non-Formulary / Non-Preferred Brand
- Eprosartan / HCT (Teveten®/ HCT) – Non-Formulary / Non-Preferred Brand
- Irbesartan / HCT (Avapro® / HCT) – Non-Formulary / Non-Preferred Brand
- Olmesartan / HCT (Benicar®) – Non-Formulary / Non-Preferred Brand
- Telmisartan /HCT(Micardis®) – Non-Formulary / Non-Preferred Brand

Angiotensin Converting Enzyme (ACE) Inhibitor Therapy includes the following drugs:

- Benazepril / HCT (Lotensin®) – Generic Preferred
- Captopril / HCT (Capoten®) – Generic Preferred
- Enalapril / HCT (Vasotec®) – Generic Preferred
- Fosinopril / HCT (Monopril®) – Generic Preferred
- Lisinopril / HCT (Prinivil/ Zestril®) – Generic Preferred
- Moexipril / HCT (Univasc®)– Generic Preferred
- Quinapril / HCT (Accupril®) – Generic Preferred
- Ramipril / HCT (Altace®) – Generic Preferred
- Trandolapril / HCT (Mavik®) – Generic Preferred
- Perindopril / HCT (Aceon®) – non-formulary / non-preferred brand

General Background

FDA Approved Indications

Seven oral angiotensin II receptor blockers (ARBs) are available in the United States: candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, and valsartan. The drugs are labeled for the treatment of hypertension, heart failure, diabetic nephropathy, and reducing mortality and morbidity due to cardiovascular disease. They are used off-label to reduce proteinuria in non-diabetic nephropathy and to reverse left ventricular hypertrophy.

According to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7), most hypertensive patients will require two or more antihypertensive medications to achieve their blood pressure (BP) goals. For most patients without compelling indications, thiazide-type diuretics used as initial therapy either alone or in combination with with drugs from other classes. In patients with compelling indications, the use of other antihypertensive drug classes [angiotensin-converting enzyme inhibitors (ACEIs), angiotensin-receptor blockers (ARBs), beta blockers (BBs), calcium channel blockers (CCBs)] will be required to achieve goal BP. However, two or more antihypertensive medications may be required in patients with diabetes and chronic kidney disease.

Many head-to-head trials have compared the ARBs with each other for mild-to-moderate hypertension. The individual ARBs have equivalent efficacy for controlling blood pressure, whether used alone or in combination with a diuretic. No dose algorithms are currently available for switching between agents. Similar numbers of patients respond to ARBs, reaching a diastolic blood pressure (DBP) less than 90 mmHg or at least a 10 mmHg reduction from baseline. Clinical trials found the following response rates with monotherapy: Candesartan 53–55%, Irbesartan 53–64%, Losartan 48–56%, and Valsartan 49–56% (not reported for eprosartan, olmesartan, telmisartan). ARB monotherapy reduces DBP 6.2–11.5 mmHg: Candesartan 8.9–9.5 mmHg, Eprosartan 6.2 mmHg, Irbesartan 8.7–10.4 mmHg, Losartan 8.2–10 mmHg, Olmesartan 11.5, Telmisartan 8.5 mmHg, and Valsartan 7.9–9.5 mmHg. Monotherapy reduces SBP

8.4–14.7 mmHg. In combination with a diuretic, ARBs reduce DBP 8.5–13.6 mmHg and SBP 11.6– 0.6 mmHg.

No published trials have compared the individual ARBs with each other in the elderly, children, renal failure, or poorly-controlled hypertension. No differences were noted between the individual ARBs in patients of African American descent. In patients of Asian descent, candesartan, irbesartan, and losartan have equivalent efficacy; telmisartan may lower blood pressure more than losartan, although overall response rates are similar. In patients with diabetes and hypertension, DBP was lowered more by telmisartan (8 mmHg) than eprosartan (4 mmHg), although SBP was reduced to a similar extent by both agents.

Monotherapy with ARBs or ACEIs is equally efficacious in the elderly, African Americans, diabetics, renal failure, and poorly-controlled hypertension. When patients given additional hydrochlorothiazide are included in study analyses, response rates may be higher with ARBs than ACEIs. The ARBs may be more effective than ACEIs in patients of Asian descent.

Five trials have compared ARBs (candesartan, telmisartan) and ACEIs (enalapril, lisinopril, perindopril, ramipril) in patients with diabetes and hypertension. Rosei et al. reported similar blood pressure lowering with candesartan (16/8 mmHg) and enalapril (17/6 mmHg, NS vs. candesartan). Blood pressure was reduced below 130/85 in similar numbers of patients given candesartan (64%) or enalapril monotherapy (62%). In a trial that did not allow dose titration, DBP was lowered more with perindopril (11 mmHg) than candesartan (8 mmHg), although the two drugs reduced SBP a similar amount (perindopril 13 mmHg, candesartan 12 mmHg). The third trial found no difference between telmisartan and ramipril, although neither agent had a significant effect on blood pressure. The combination of telmisartan and ramipril was no more effective than either agent alone. Similarly, two trials found no significant benefit when candesartan was added to existing lisinopril therapy, although these trials may have been underpowered to detect small treatment differences.

In a systematic review which included 61 randomized and observational studies that directly compared ACE inhibitors versus ARBs in adult patients with essential hypertension, Matchar, et al (2008) reported that the two drug classes are about equally safe and effective at managing high blood pressure and have similar effects on other risk factors and clinical outcomes in patients with essential hypertension. This assessment also confirmed that ARBs are less likely to cause coughing.

Five individual clinical trials compared the efficacy of ARBs (losartan, telmisartan) and ACEIs (captopril, enalapril, trandolapril) in patients with renal failure. Three individual clinical trials evaluated the efficacy of ARBs (candesartan, losartan, valsartan) added to ACEIs (benazepril, enalapril, lisinopril, perindopril, ramipril, trandolapril) compared with ACEIs or ARBs alone. One individual clinical trial has evaluated the efficacy of two individual ARBs. However, this study was not included because it presented only pooled results and did not make any comparisons between treatment groups.

Based on the few available studies, the ARBs and the ACEIs have equivalent efficacy in patients with renal failure. Combination therapy with an ARB and an ACEI is more efficacious than ARB monotherapy. One trial of 108 patients found combination therapy more effective than ACEI monotherapy. A second, smaller study (n=16) found no difference between combination therapy and ACEI monotherapy but may have lacked sufficient statistical power to detect existing differences.

The ARBs and calcium channel blockers have equivalent efficacy in the elderly and children. The ARBs may be less effective than calcium channel blockers in patients of Asian descent. In patients with poorly-controlled hypertension, combining an ARB plus an ACEI may be less effective than combining an ARB plus a calcium channel blocker.

Heart Failure: No trials are available comparing the ARBs with each other for this use. Monotherapy with ARBs or ACEIs improves survival and heart-failure-related hospitalizations. Compared with ACEI monotherapy, the combination of an ARB and an ACEI does not alter survival, although it may reduce hospitalizations

Diabetic nephropathy accounts for 40% of new end-stage renal disease (ESRD) in the United States. Fewer patients with type 2 diabetes progress to ESRD than patients with type 1 diabetes, although 20–30% of all patients with diabetes (type 1 or 2) will develop evidence of nephropathy. To reduce the risk or slow the progression of nephropathy, the American Diabetes Association (ADA) recommends optimizing glucose control. For patients with nephropathy, the ADA recommends optimizing glucose control and treatment with an ACEI or an ARB. Evidence shows that both ACEIs and ARBs can slow the progression of nephropathy in patients with type 2 diabetes. There is no current evidence that ARBs slow the progression of nephropathy in patients with type 1 diabetes, although the ADA recommends substituting between the ACEIs and ARBs if one class is not tolerated. Restricting protein intake to the current adult recommended daily allowance (RDA) may also be of some benefit in patients with nephropathy. There is some evidence that calcium channel blockers may be efficacious in patients with diabetic nephropathy; however, these agents are currently not recommended as first-line therapy by the ADA.

Losartan and olmesartan were equally effective at reducing albuminuria in 19 patients with diabetic nephropathy and hypertension. Monotherapy with ARBs or ACEIs reduces urinary albumin excretion to a similar extent. Compared with monotherapy, the combination of an ARB and ACEI may further reduce albuminuria. The ARBs reduce albuminuria and slow the progression of diabetic nephropathy more than amlodipine. The risk of doubling serum creatinine was significantly reduced by irbesartan (RR 0.63, 95% CI 0.48–0.81, $p < 0.001$ vs. amlodipine). Urinary albumin excretion was more likely to be normal after irbesartan therapy (30%) than amlodipine (14%, $p < 0.001$).

Non-diabetic nephropathy is less common, accounting for less than 20% of new ESRD cases, and encompasses a wide variety of disorders, including glomerular, vascular, tubulointerstitial, and cystic diseases. The degree of proteinuria differs between the specific disorders but is typically higher in the glomerular disorders. The Kidney Disease Outcomes Quality Initiative (K/DOQI) recommends ACEIs as first-line therapy to slow the progression of non-diabetic nephropathy. Because less evidence is available, the ARBs are not recommended first-line agents but may be considered in patients who cannot tolerate ACEIs. Additional study is needed to determine whether combination therapy with ACEIs and ARBs is more effective than monotherapy with either class. Restricting protein intake may also be of benefit, although the optimal level remains unknown.

In non-diabetic nephropathy, proteinuria was reduced more with candesartan (49%) than losartan (36%, $p < 0.01$) in the single trial comparing individual ARBs. Monotherapy with ARBs or ACEIs reduces urinary albumin excretion to a similar extent. In one long-term trial, the risk of the composite endpoint (end-stage renal disease or doubling of serum creatinine) was lower with combination therapy than either ARB monotherapy (HR 0.4, 95% CI 0.17–0.69, $p = 0.016$) or ACEI monotherapy (HR 0.38, 95% CI 0.18–0.63, $p = 0.018$).

In the setting of chronic kidney disease (CKD), a meta-analysis study reported by Kunz R, et al (2008) evaluated 49 randomized trials of ARBs versus placebo, ACE inhibitors, calcium-channel blockers, or the combination of ARBs and ACE inhibitors in patients with or without diabetes and with microalbuminuria or proteinuria. Data showed that ARBs were more effective than calcium-channel blockers and ACE inhibitor and ARB monotherapy are similarly effective at reducing proteinuria, but a combination of the two angiotensin-2-suppressing drugs works better than either agent individually, however, the safety of such combination therapy is largely undefined.

In a multicenter, randomized, double-blind, placebo-controlled paralleled group study [Irbesartan in the Management of PROteinuric patients at high risk for Vascular Events (IMPROVE)], Bakris et al (2007) reported that more patients on dual therapy, ramipril plus irbesartan, achieved target blood pressure goals at week 20 than with ramipril plus placebo. However, the change in albumin excretion rate for ramipril plus irbesartan and ramipril plus placebo were not significantly different. Incidence of adverse effects and treatment-related adverse effects was similar in both groups.

Left Ventricular Hypertrophy: Left ventricular mass index decreased a similar extent with losartan (14%) and telmisartan (12%) in one small study ($n = 30$). The ARBs are at least as effective as ACEIs or atenolol at inducing hypertrophy regression. However, the ARBs are more efficacious than amlodipine or diuretics.

Reducing Morbidity and Mortality due to Cardiovascular Disease: No clinical trials have compared the individual ARBs with each other for this use. The LIFE study was a landmark trial that established the superiority of losartan over atenolol for improving long-term outcomes. However, each ARB evaluated in clinical trials has reduced cardiovascular morbidity and mortality, including candesartan, eprosartan, irbesartan, losartan, and valsartan. No trials have evaluated the effects of olmesartan or telmisartan.

The ARBs are beneficial in a diverse group of at-risk patients including the elderly, African Americans with hypertension and left ventricular hypertrophy; Japanese patients with hypertension; and Japanese patients with hypertension and chronic renal disease. ARBs are also effective in patients with hypertension, coronary artery disease, isolated systolic hypertension, isolated systolic hypertension and left ventricular hypertrophy, hypertension and recent stroke, hypertension and diabetes, hypertension and type 2 diabetes with nephropathy, hypertension and diabetes mellitus with left ventricular hypertrophy, hypertension and left ventricular hypertrophy, hypertension and left ventricular hypertrophy without preexisting vascular disease, acute myocardial infarction accompanied by heart failure or anterior Q-wave infarction, or acute myocardial infarction accompanied by left ventricular dysfunction or heart failure.

Comparative trials evaluating the ARBs in hypertension found no differences between the agents in adverse effects. The ARBs are less likely than the ACEIs to cause cough or angioedema. Patients treated with ARB/ACEI combination therapy may be more likely to discontinue therapy due to adverse events than those given ACEI monotherapy.

Pharmacodynamic interactions may occur with any ARB, including increased hypotension with diuretics, increased risk of hyperkalemia with potassium supplements or potassium-sparing diuretics, and lithium toxicity. The effects of irbesartan may be increased by agents that inhibit hepatic cytochrome P450 (CYP450). Since formation of the active metabolite is altered, the effects of losartan may be reduced by agents that inhibit CYP450 and increased by agents that induce CYP450. Telmisartan may increase risk of digoxin toxicity.

The available evidence does not suggest the ARBs have any efficacy advantage over the ACEIs for the included therapeutic uses. The ARBs are considered first-line therapy for hypertensive patients with diabetes mellitus (type 1 or 2) with proteinuria, hypertensive patients with chronic kidney disease, and patients with diabetic nephropathy (may choose either ARB or ACEI). In patients who cannot tolerate ACEIs, the ARBs are recommended for those with hypertension and compelling indications, patients with heart failure, and patients with non-diabetic nephropathy. The ARBs are less likely than the ACEIs to cause cough or angioedema. However, angioedema has been reported with ARBs in patients with a history of ACEI-associated angioedema.

Current disease treatment guidelines do not recommend combination therapy with ARBs and ACEIs for any of the included therapeutic uses. However, based on evidence from clinical trials, combination therapy may be appropriate in patients with diabetic nephropathy or non-diabetic nephropathy. Additional study is needed to determine whether the combination improves outcomes in patients with heart failure. Findings from current published studies suggest that the monotherapy with inhibitors of the renin-angiotensin system is sufficient for patients with early-stage renal disease and relatively low albumin excretion and that combination therapy is effective for patients with heavier proteinuria. However, no safety data is available for the combination therapy in chronic kidney disease. Patients treated with combination therapy may be more likely to discontinue therapy due to adverse events than those given ACEI monotherapy.

Coding/Billing Information

Note: not applicable for this coverage position.

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