



# CIGNA HEALTHCARE COVERAGE POSITION

**Subject: Angiotensin II Receptor Blocker Therapy**

**Coverage Position Number: 4009**

**Effective Date: 4/15/2004**

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## 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. ©2004 CIGNA Health Corporation

## Coverage Position

**Angiotensin II Receptor Blocker 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

**CIGNA HealthCare covers Angiotensin II Receptor Blocker Therapy when the following medical necessity criteria are met:**

- failure, contraindication, or intolerance to ACE-Inhibitor therapy

## General Background

*The following information is abstracted from a larger drug review monograph.*

Seven angiotensin II receptor blockers (ARBs) are available in the US: candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, and valsartan. This review will focus on the therapeutic use of the ARBs in hypertension, heart failure, diabetic nephropathy, and left ventricular hypertrophy (LVH).

The ARBs act on the renin-angiotensin-aldosterone (RAA) system to exert their antihypertensive effects.<sup>1</sup> The angiotensin-converting enzyme inhibitors (ACEIs) also act on the RAA system, albeit by a different

mechanism. The ACEIs prevent the conversion of angiotensin I to angiotensin II, by binding reversibly with angiotensin converting enzyme (ACE).<sup>2</sup> The ARBs reversibly inhibit the binding of angiotensin II to angiotensin subtype 1 (AT<sub>1</sub>) receptors.<sup>1</sup> Similar to the ACEIs, the ARBs decrease peripheral vascular resistance without increasing heart rate.<sup>3, 4</sup>

The RAA system helps regulate arterial pressure, both acutely and chronically.<sup>1</sup> Renin is released from the kidney in response to apparent decreases in arterial pressure, blood volume, and total peripheral resistance, as well as other stimuli. Renin catalyzes the formation of angiotensin I from angiotensinogen. Angiotensin I is later converted to angiotensin II by angiotensin converting enzyme (ACE). Acutely, angiotensin II stimulates AT<sub>1</sub> receptors, which increases arterial pressure and inhibits further renin release. Cardiac preload and afterload increase, both acutely and chronically.<sup>1</sup> Other chronic effects of angiotensin II include ventricular hypertrophy, reduced vessel wall compliance,<sup>5</sup> and aldosterone production and secretion.<sup>1, 4</sup> Many head-to-head trials have been conducted between the ARBs in patients with hypertension. However, no data exist for establishing equivalent doses for switching between agents. The dosage of each agent must be titrated for the individual patient to achieve maximal efficacy.

## Hypertension

Hypertension, the second most common risk factor for cardiovascular disease, affects over 30 million Americans.<sup>82</sup> Disease prevalence increases after the age of 30 years and is higher in minorities than in the general population. In African-Americans, hypertension occurs at an earlier age and is more severe. Hypertension may progress to LVH and heart failure if left untreated, in addition to increasing the risk of atherosclerosis and nephrosclerotic renal failure.<sup>82</sup>

The ARBs are not considered first-line agents for treating hypertension in the general population.<sup>83</sup> However, the ARBs are useful for specific patients who cannot tolerate therapy with ACEIs. The sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI) recommends ACEIs as first-line agents in hypertensive patients with diabetes mellitus (type 1 or 2) with proteinuria, heart failure, or after myocardial infarction.<sup>83</sup> The 1999 WHO/ISH Hypertension guidelines recommend either an ARB or an ACEI for patients with heart failure. The 2001 Canadian recommendations for high blood pressure advocate an ACEI or and ARB as first line therapy for patients with diabetes mellitus (type 1 or 2) with nephropathy.<sup>84</sup> Because many patients cannot tolerate an ACEI, it is reasonable to substitute an ARB in patients with these conditions who cannot tolerate ACEIs.<sup>85</sup> Additionally, there is some evidence that first-line therapy with an ARB can decrease the number of clinic visits required because no additional visits are required to manage adverse effects.<sup>82</sup>

Similar to the ACEIs, the ARBs can be added as a second or third agent for patients with inadequate blood pressure lowering during monotherapy. Because only 50% of patients achieve a blood pressure below 140/90 mmHg with a single agent, the ACEIs and ARBs may provide the additional hypotensive effect necessary to lower cardiac risk.<sup>86</sup> In diabetic patients, blood pressure should be lowered below 130/80 mmHg.<sup>87</sup>

## Heart Failure

Heart failure is a common disorder, affecting almost 5 million Americans.<sup>91, 92</sup> Between 400,000 to 700,000 cases are diagnosed annually. Prevalence increases with age, affecting almost 10% of Americans in their 80s. Each year, heart failure accounts for more than 3 million hospitalizations, 12-15 million office visits, and up to 350,000 deaths, either directly or indirectly. The direct medical costs are more than \$20 billion annually.<sup>91, 92</sup>

The most current treatment guidelines recommend combination therapy with a diuretic, an ACEI, a beta-adrenergic blocker, and digoxin for routine management.<sup>91, 92</sup> Spironolactone, ARBs, hydralazine, and isosorbide dinitrate are not recommended for routine use but may be beneficial in specific patient subgroups. Spironolactone may be used in patients with Class IV symptoms, provided renal function and potassium concentrations are normal. The ARBs are considered an alternative in patients who cannot tolerate therapy with an ACEI due to cough or angioedema. Combination therapy with hydralazine and isosorbide dinitrate is recommended when ACEIs are contraindicated due to hypotension or renal

insufficiency. An ARB may be used in conjunction with an ACEI although there is less evidence to support the efficacy of this combination. Patients with refractory heart failure are treated similarly but should also be referred for cardiac transplantation when appropriate.<sup>91, 92</sup>

### Diabetic Nephropathy

Diabetic nephropathy accounts for 40% of new end-stage renal disease (ESRD) in the United States.<sup>93</sup> Fewer patients with type 2 diabetes progress to ESRD than patients with type 1 diabetes, although 20 to 30% of all patients with diabetes (type 1 or 2) will develop evidence of nephropathy.<sup>93</sup> The cost of treating diabetic patients with ESRD was more than \$15.6 billion dollars in 1997.<sup>93</sup> 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.<sup>93, 94</sup> 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.<sup>93</sup> Restricting protein intake to the current adult recommended daily allowance (RDA) may also be of some benefit in patients with nephropathy.<sup>93</sup> 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.<sup>94, 95</sup>

### Left Ventricular Hypertrophy

Left ventricular hypertrophy, which results from long-standing hypertension, is a marker for increased cardiovascular morbidity and mortality.<sup>99-101</sup> Most antihypertensive agents reduce LVH to some degree, however the ACEIs and ARBs are the most widely studied for this purpose.<sup>101</sup> Levy, et al.<sup>99</sup> first described the prognostic implications of LVH in 1990 based on results of the Framingham Heart Study. These data showed that LVH can increase the risk of cardiovascular morbidity and death after adjustment for other cardiac risk factors such as age, cholesterol profile, electrocardiographic evidence of LVH, smoking, diabetes, obesity, blood pressure, and treatment of hypertension.<sup>99, 100</sup> Healthy patients with LVH (>143 g/m<sup>2</sup> for men and >102 g/m<sup>2</sup> for women) followed for 4 years had a relative risk of cardiovascular death of 1.73 for men and 2.12 for women, compared to patients without LVH. The relative risk of all-cause mortality was also higher in those with LVH (1.49 for men and 2.01 for women).<sup>99</sup>

Results from the LIFE study<sup>73</sup> question the use of LVH as a marker for increased cardiovascular morbidity and mortality.<sup>102</sup> These authors found no difference in cardiovascular mortality with losartan despite LVH regression.<sup>73</sup> Additional study is needed to determine the true value of LVH reduction in reducing morbidity and mortality.

### Summary

Seven ARBs are available in the U.S. for therapeutic use: candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, and valsartan. Several head-to-head trials have been conducted between the individual ARBs in patients with hypertension. Since limited data are available to suggest that efficacy differences exist between the individual ARBs, treatment decisions must be based on other factors, including side effects, patient preference and cost.

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## Coding/Billing Information

**Note:** This list of codes may not be all-inclusive.

**Covered when medically necessary:**

| CPT <sup>®</sup> * Codes | Description |
|--------------------------|-------------|
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| HCPCS Codes | Description |
|-------------|-------------|
|             |             |

| ICD-9-CM Diagnosis Codes | Description |
|--------------------------|-------------|
|                          |             |

**Experimental/Investigational/Unproven/Not Covered:**

| CPT* Codes | Description |
|------------|-------------|
|            |             |

| HCPCS Codes | Description |
|-------------|-------------|
|             |             |

| ICD-9-CM Diagnosis Codes | Description |
|--------------------------|-------------|
|                          |             |

**\*Current Procedural Terminology (CPT®) ©2003 American Medical Association: Chicago, IL.**

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*The following lists the complete references used within a larger drug review monograph. To obtain a copy of the full drug review monograph, please contact the Pharmacy Service Center at 800.832.3211.*

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