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Angiotensin II Receptor Antagonist/ Calcium Channel Blocker Combinations Step Therapy Criteria

Brand	Generic	Dosage Form
Azor [®]	amlodipine/olmesartan medoxomil	oral tablets
Exforge [®]	amlodipine/valsartan	oral tablets
Exforge HCT [®]	amlodipine/valsartan/hydrochlorothiazide	oral tablets

FDA-APPROVED INDICATIONS^{1,2}

Azor[®]¹

Azor[®] (amlodipine and olmesartan medoxomil) is indicated for the treatment of hypertension, alone or with other anti-hypertensive agents. This fixed combination drug is not indicated for the initial therapy of hypertension.

Exforge[®]²

Exforge[®] (amlodipine and valsartan) is indicated for the treatment of hypertension. This fixed combination drug is not indicated for the initial treatment of hypertension.

Exforge HCT[®]⁴⁰

Exforge[®] (amlodipine and valsartan) is indicated for the treatment of hypertension. This fixed combination drug is not indicated for the initial treatment of hypertension.

RATIONALE FOR STEP THERAPY

The intent of the Angiotensin II Receptor Antagonist/Calcium Channel Blocker Combinations Step Therapy criteria is to promote the use of cost-effective generic angiotensin converting enzyme inhibitors (ACEIs) or generic ACEI combinations (ACEI/diuretic or ACEI/CCB) before a brand angiotensin II receptor antagonist (ARB)/Calcium Channel Blocker (CCB) combination.

Azor (amlodipine/olmesartan)

Azor was FDA approved based on one placebo-controlled trial.^{1,3} An 8-week multicenter, randomized, double-blind, placebo controlled, parallel group factorial study in patients with mild to severe hypertension was conducted to determine if treatment with Azor was associated with clinically significant reduction in blood pressure compared to the respective monotherapies.¹ The study randomized 1,940 patients equally to one of the following 12 treatment arms: placebo, monotherapy with amlodipine 5 mg or 10 mg, monotherapy with olmesartan 10 mg, 20 mg, or 40 mg, or combination therapy with amlodipine/olmesartan doses of 5/10 mg, 5/20 mg, 5/40 mg, 10/10 mg, 10/20 mg, and 10/40 mg monotherapy components. Primary and one of the secondary endpoints were mean change from baseline in seated diastolic and seated systolic blood pressure at week 8, respectively. Results showed that amlodipine 10 mg/day plus olmesartan 40 mg/day reduced systolic blood pressure an average of 30.1 mm Hg and the diastolic reading an average of 19.0 mm Hg. These results compared to mean reductions of 19.7 mm Hg systolic/12.7 mm Hg diastolic for amlodipine 10 mg alone, 16.1 mm Hg systolic/10.2 mm Hg diastolic for olmesartan 40 mg alone, and 4.8 mm Hg systolic/3.1 mm Hg diastolic for placebo. When compared to amlodipine 10 mg alone, amlodipine 10 mg/day plus olmesartan 40

mg/day caused a 53% greater reduction in systolic blood pressure. Reductions from baseline in blood pressure were progressively greater with increases in dose of both amlodipine and olmesartan components of Azor.^{1,3}

The antihypertensive effect of Azor was similar in patients with and without prior antihypertensive medication use, in patients with and without diabetes, in patients ≥ 65 years of age and < 65 years of age, and in women and men.¹ Azor was effective in treating black patients (usually a low-renin population), and the magnitude of blood pressure reduction in black patients approached that observed for non-black patients.¹ The adverse event profile for each of the combinations was similar in nature to the monotherapy components. All combinations with amlodipine 10 mg demonstrated a lower incidence of edema versus amlodipine 10 mg monotherapy. Most reported adverse events across all treatment groups were considered mild in severity.^{1,3}

Upon completing the 8-week, double-blind, placebo-controlled study, 1,684 patients entered a 44-week open-label extension and received combination therapy with amlodipine 5 mg plus olmesartan 40 mg. During the open-label extension, patients whose blood pressure was not adequately controlled (i.e., did not achieve a blood pressure goal of $< 140/90$ mm Hg, or $< 130/80$ mm Hg for those patients with diabetes) on amlodipine/olmesartan 5/40 mg were titrated to amlodipine/olmesartan 10/40 mg. Patients whose blood pressure was still not adequately controlled were offered additional hydrochlorothiazide 12.5 mg and subsequently 25 mg as required to achieve adequate blood pressure goal. A total of 80.0% of patients on amlodipine/olmesartan 5/40 mg reached their blood pressure treatment goal at 52 weeks of treatment. Those patients who required titration of the amlodipine dose or the addition of hydrochlorothiazide were more severe hypertensive patients and/or were more resistant to the antihypertensive effects of treatment and had a lower percentage of patients achieving blood pressure goals (46% – 71%).^{1,3}

The adverse event profile obtained from the 44 weeks of open-label combination therapy was similar to that observed during the 8-week, double-blind, placebo-controlled period. No new safety issues were identified during the course of this study. Edema was the most common drug-related adverse event and was experienced by 19% of patients.^{1,3}

Exforge (amlodipine/valsartan)

Exforge was FDA approved based on two unpublished, placebo-controlled and two unpublished active-controlled trials in hypertensive patients.² One double-blind, placebo controlled study in patients with mild-to-moderate hypertension (N=1,018) compared 3 combinations of amlodipine and valsartan (5/80, 5/160, 5/320), to amlodipine alone (5 mg), valsartan alone (80, 160, or 320 mg) or placebo. At week 8, the combination treatments were statistically significantly superior to their monotherapy components in reduction of diastolic and systolic blood pressures.² Results showed that amlodipine 5 mg/day plus valsartan 320 mg/day reduced systolic blood pressure an average of 22.4 mm Hg and the diastolic reading an average of 15.7 mm Hg. These results are compared to mean reductions of 14.8 mm Hg systolic/11.1 mm Hg diastolic for amlodipine 5 mg alone, 16.3 mm Hg systolic/13.2 mm Hg diastolic for valsartan 320 mg alone, and 6.2 mm Hg systolic/6.4 mm Hg diastolic for placebo. The second double-blind, placebo controlled study in patients with mild-to-moderate hypertension (N=1,250) compared treatment of 2 combinations of amlodipine and valsartan (10/160, 10/320 mg) to amlodipine alone (10 mg), valsartan alone (160 or 320 mg) or placebo. At week 8, the combination treatments were statistically significantly superior to their monotherapy components in reduction of diastolic and systolic blood pressures.² Results showed that amlodipine 10 mg/day plus valsartan 320 mg/day reduced systolic blood pressure an average of 26.9 mm Hg and the diastolic reading an average of 18.1 mm Hg. These results compare to mean reductions of 22.2 mm Hg systolic/15.0 mm Hg diastolic for amlodipine 10 mg alone, 18.5 mm Hg systolic/12.8 mm Hg diastolic for valsartan 320 mg alone, and 11.0 mm Hg systolic/8.2 mm Hg diastolic for placebo.²

Philipp et al.⁴ reported the results from the two placebo-controlled studies conducted to evaluate efficacy as well as safety and tolerability. The 2 studies were multinational, multicenter, 8-week, randomized, double-blind, placebo-controlled, parallel-group trials. In study 1, patients were randomized to receive amlodipine 2.5 or 5 mg once daily, valsartan 40 to 320 mg once daily, the combination of amlodipine 2.5 or 5 mg with valsartan 40 to 320 mg once daily, or placebo. In study 2, patients were randomized to

receive amlodipine 10 mg once daily, valsartan 160 or 320 mg once daily, the combination of amlodipine 10 mg with valsartan 160 or 320 mg once daily, or placebo. The primary efficacy variable in both studies was change from baseline in mean sitting diastolic blood pressure (MSDBP) at the end of the study. Secondary variables included the change in mean sitting systolic blood pressure (MSSBP), response rate (the proportion of patients achieving an MSDBP <90 mm Hg or a ≥ 10 -mm Hg decrease from baseline), and control rate (the proportion of patients achieving an MSDBP <90 mm Hg). Safety was assessed in terms of adverse events (spontaneously reported or elicited by questioning), vital signs, and laboratory values.⁴

A total of 1,911 patients were randomized to treatment in study 1; 1,250 were randomized to treatment in study 2. The overall baseline mean sitting BP was 152.8/99.3 mm Hg in study 1 and 156.7/99.1 mm Hg in study 2. The reported results showed that with the exception of a few combinations that included amlodipine 2.5 mg, the combination regimens in both studies were associated with significantly greater reductions in MSDBP and MSSBP compared with their individual components and placebo ($p < 0.05$). A positive dose response was observed for all combinations. The highest response rate in study 1 was associated with the highest dose of combination therapy (amlodipine 5 mg + valsartan 320 mg: 91.3%). Amlodipine 5 mg, valsartan 320 mg, and placebo were associated with response rates of 71.9%, 73.4%, and 40.9%, respectively. In study 2, the 2 doses of combination therapy were associated with similar response rates (amlodipine 10 mg + valsartan 160 mg: 88.5%; amlodipine 10 mg + valsartan 320 mg: 87.5%). Amlodipine 10 mg was associated with a response rate of 86.9%; valsartan 160 and 320 mg were associated with response rates of 74.9% and 72.0%, respectively; and placebo was associated with a response rate of 49.3%. Control rates followed a similar pattern. The incidence of peripheral edema with combination therapy was significantly lower compared with amlodipine monotherapy (5.4% vs 8.7%, respectively; $p = 0.014$), was significantly higher compared with valsartan monotherapy (2.1%; $p < 0.001$), and did not differ significantly from placebo (3.0%).⁴

Active control studies compared the amlodipine/valsartan combination to each of the individual ingredients. A double-blind, active-controlled study in patients with mild-to-moderate hypertension who were not adequately controlled on valsartan 160 mg ($n=947$) compared the treatment of 2 combinations of amlodipine and valsartan (10/160, 5/160), to valsartan alone (160 mg). A second double-blind, active-controlled study in patients with mild-to-moderate hypertension who were not adequately controlled on amlodipine 10 mg received a combination of amlodipine and valsartan (10/160 mg) to amlodipine alone (10 mg). In both trials, at week 8, the combination treatment was statistically significantly superior to the monotherapy component in reduction of diastolic and systolic blood pressures.² In the first, results showed that amlodipine 10 mg/day plus valsartan 160 mg/day reduced systolic blood pressure an average of 13.9 mm Hg and the diastolic reading an average of 11.4 mm Hg, in comparison with mean reductions of 8.2 mm Hg systolic/6.6 mm Hg diastolic for valsartan 160 mg alone; results from the second study showed mean reductions of 12.7 mm Hg systolic/11.8 mm Hg diastolic for amlodipine 10 mg/day plus valsartan 160 mg/day compared to mean reductions of 10.8 mm Hg systolic/10.0 mm Hg diastolic for amlodipine 10 mg alone.²

Exforge HCT (amlodipine/valsartan/hydrochlorothiazide)

Exforge HCT was studied in a double-blind, active controlled study in hypertensive patients. A total of 2,271 patients with moderate to severe hypertension (mean baseline systolic/diastolic blood pressure was 170/107 mmHg) received treatments of amlodipine/valsartan/HCTZ 10/320/25 mg, valsartan/HCTZ 320/25 mg, amlodipine/valsartan 10/320 mg, or HCTZ/amlodipine 25/10 mg. At study initiation patients assigned to the two-component arms received lower doses of their treatment combination while patients assigned to the Exforge HCT arm received 160/12.5 mg valsartan/hydrochlorothiazide. After one week, Exforge HCT patients were titrated to 5/160/12.5 mg amlodipine/valsartan/hydrochlorothiazide, while all other patients continued receiving their initial doses. After two weeks, all patients were titrated to their full treatment dose. A total of 55% of patients were male, 14% were 65 years or older, 72% were Caucasian, and 17% were Black. At week 8, the triple combination therapy produced greater reductions in blood pressure than each of the three dual combination treatments ($p < 0.0001$ for both diastolic and systolic blood pressures reductions). The reductions in systolic/diastolic blood pressure with Exforge HCT were 7.6/5.0 mmHg greater than with valsartan/HCTZ, 6.2/3.3 mmHg greater than with amlodipine/valsartan, and 8.2/5.3 mmHg greater than with amlodipine/HCTZ. The full blood pressure lowering effect was achieved 2 weeks after being on the maximal dose of Exforge HCT.

Treatment of 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.^{5,6} Multiple outcome trials with ACEIs in the treatment of hypertension have been conducted. Two outcome trials, ALLHAT⁷ and ANBP2,⁸ are particularly important in establishing ACEIs 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 hypertension.⁹⁻¹²

The Agency for Healthcare Research and Quality (AHRQ)¹³ 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)¹⁴ 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.¹⁴ The guidelines suggest that CCBs have a compelling indication, unless contraindicated (long-acting dihydropyridine), for high coronary disease risk and also patients with type 1 and type 2 diabetes.¹⁴ These guidelines state that many patients with hypertension will require more than one drug to control blood pressure.¹⁴

Guidelines from the American Diabetes Association (ADA)¹⁵ 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.¹⁵

In the United Kingdom (National Institute for Clinical Excellence: NICE, 2006) hypertension guidelines recommend the following pharmacotherapy for treatment of hypertension. In hypertensive patients aged ≥ 55 or black patients (African or Caribbean descent) of any age, the first choice for initial therapy

should be either a calcium channel blocker or a thiazide diuretic. In hypertensive patients of age <55, the first choice for initial therapy should be an ACEI (or ARB if an ACEI is not tolerated). If blood pressure remains uncontrolled with the first drug, second step therapy is an ACEI plus calcium channel blocker or ACEI plus thiazide diuretic.¹⁶

Safety and Tolerability

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.¹⁷ There was little evidence of meaningful differences in tolerability profiles for the agents.¹⁷ As a class, ARBs are also well tolerated, with adverse events profiles for the agents generally similar to placebo,^{17,18} though large placebo-controlled trials have found more discontinuations due to adverse events with ARBs.^{19,20} 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.²¹⁻²⁴ Although the rate of angioedema appears to be lower with ARBs than ACEIs, the rates are low for each class.²⁴ 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.^{25,26}

Lisinopril, enalapril and captopril have the most outcome data of the class of ACEIs. However, seven sets of clinical guidelines (JNC 7¹⁴, European Society of Cardiology/European Society of Hypertension²⁷, AHA/ACC²⁸, British Hypertension Society²⁹, National Kidney Foundation³⁰, American Diabetes Association¹⁵, Agency for Healthcare Research and Quality [AHRQ]¹³) consider all drugs in this class equal in the treatment of each of the FDA approved indications.

The use of ACEIs and ARBs for indications other than hypertension is supported by guidelines for treatment of heart failure, left ventricular dysfunction, post-myocardial infarction, coronary artery disease, diabetic nephropathy and renal disease.^{28,31-36} 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.³⁷⁻³⁹ 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.

Therefore, the *PA Criteria for Approval* for ARB/CCB combinations will require that patients try and fail an ACEI or ACEI combination prior to administration of the ARB/CCB combination product, unless the patient has an allergy, intolerance or contraindication to the ACEI products.

Step Therapy Electronic Edit

The intent of the initial step therapy edit is to electronically identify patients and automatically pay for drug claims for a brand ARB/CCB combination if there is a prior medication history for the identical drug or another product containing the identical ARB (single ingredient or combination). 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 a brand ARB/CCB combination, the step therapy edit will automatically pay if the patient has a medication history of a generic ACEI or generic ACEI combination (ACEI/diuretic or ACEI/CCB) in the previous 90 days. ARBs and ARB combinations are not preferred over ACEIs and ACEI combinations, 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 ARB/CCB combination will be paid if the patient used that identical product or another product containing the identical ARB (single ingredient or combination) within the past 90 days. Claims for a brand ARB/CCB combination will also be approved if there is a history of use or if the patient has tried a generic ACEI or ACEI combination and discontinued due to failure, allergy, intolerance, or contraindication to the agent.

INITIAL AUTOMATIC STEP THERAPY EDIT FUNCTIONALITY

The overall process for step therapy requires that another drug or drugs be tried in a designated time period before the claim drug. The patient must have evidence of the applicable drug-specific edit(s) in the patient's prescription drug history for the automatic payment of the submitted claim. If the patient does not meet the step edit criteria, then the system will reject with the message indicating that prior authorization (PA) is necessary. The PA criteria for approval would then be applied to requests submitted by the patients' practitioner for evaluation.

New prescriptions written for a brand ARB/CCB combination will automatically pay if there is a history of the identical combination (Azor GPI 3699300205**** or Exforge GPI 3699300210**** or Exforge HCT GPI 3699450320****) or a product with the identical ARB (for Azor single ingredient olmesartan GPI 36150055***** or olmesartan/diuretic combination GPI 3699400250****; for Exforge or Exforge HCT single ingredient valsartan GPI 36150080***** or valsartan/diuretic combination GPI 3699400270****) found in the patient's medication history within the past 90 days. New claims for an ARB/CCB combination will also automatically pay if the patient's medication history contains evidence of a generic ACEI, generic ACEI/diuretic, or generic ACEI/CCB (GPI 3610*****, GPI 36991502*****, or GPI 36991802***** with multi-source code Y) within the previous 90 day look-back period. If these claims are not found, a Point of Sale Message will be returned to the pharmacy stating that step therapy criteria was not met and that a Prior Authorization approval is necessary.

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL

ARB/CCB Combination

Initial and Renewal Evaluation

1. Is the patient currently being treated with and stable on the requested ARB/CCB combination, or the requested ARB in another product (single ingredient or combination)?
If yes, approve for 12 months. If no, continue to 2.
2. Has the patient previously tried and failed therapy with a generic ACEI or generic ACEI combination?
If yes, approve for 12 months. If no, continue to 3.
3. Does the patient have an allergy, contraindication, or intolerance to an ACEI or ACEI combination?
If yes, approve for 12 months. If no, deny.

CONCLUSION

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. For instance, a brand ARB/CCB combination is automatically paid if the patient's medication history contains at least one claim for that identical brand name agent or the identical ARB in another product. A brand ARB/CCB combination is also automatically paid if the patient's medication history contains at least one claim for a generic ACEI or ACEI combination. 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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