Angiotensin II Receptor Antagonists (ARBs), Renin Inhibitors, and Combinations Step Therapy and Quantity Limit Program Summary

This program applies to FlexRx Open, FlexRx Closed, GenRx Open, Gen Closed and Health Insurance Marketplace formularies.

This is a FlexRx Standard and GenRx Standard step therapy program.

The BCBS MN Step Therapy Supplement also applies to this program for all Commercial/HIM lines of business.

### FDA APPROVED INDICATIONS AND DOSAGE

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<tr>
<th>Agents</th>
<th>HTN</th>
<th>CV Risk ↓</th>
<th>HTN/LVH</th>
<th>Post-MI</th>
<th>HF</th>
<th>DMN</th>
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<td><strong>Atacand (candesartan)</strong>*</td>
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<td><strong>Atacand HCT (candesartan/HCTZ)</strong>*</td>
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<td><strong>Avapro (irbesartan)</strong>*</td>
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<td><strong>Benicar (olmesartan)</strong>*</td>
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<td><strong>Benicar HCT (olmesartan/HCTZ)</strong>*</td>
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<th><strong>Dosing and Administration (adults)</strong></th>
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<tr>
<td><strong>HTN:</strong> Initially, 16 mg once daily, lower dose if on diuretic. May be given once or twice daily with total daily doses from 8-32 mg. Larger doses do not appear to have greater effects; limited experience with such doses. <strong>HF:</strong> Initial, 4 mg once daily. Target dose, 32 mg once daily. <strong>HTN:</strong> Candesartan/HCTZ doses ranging from 8-32 mg of candesartan with 12.5-25 mg of HCTZ were used in trials; Maximum dosage is two candesartan/HCTZ 16/12.5 mg tablets per day (32 mg/day candesartan and 25 mg/day HCTZ) given once daily. <strong>HTN:</strong> Initially, 150/12.5 mg once daily; titrate to 300/12.5 mg, then to a maximum of 300/25 mg once daily if needed. <strong>HTN:</strong> Initially, 150 mg once daily; 75 mg in volume- or salt-depleted patients. Patients requiring further BP reduction may be titrated to 300 mg once daily. Patients not adequately treated by the maximum dose of 300 mg once daily are unlikely to derive benefit from a higher dose or twice daily dosing. <strong>DMN:</strong> Initially 75 mg/day. Target dose is 300 mg/day. There are no data on clinical effects of lower doses in DMN. <strong>HTN:</strong> Initiate amlodipine/olmesartan 5/20 mg once daily (1 to 2 weeks), titrate to maximum of 10/40 mg once daily. <strong>HTN:</strong> Initially, 20 mg once daily; if volume-depleted, begin therapy with 5-10 mg once daily. Range 20-40 mg/day, given once daily. Doses &gt;40 mg/day do not appear to have greater benefit; twice daily dosing has no advantage over the same dose given once daily. <strong>HTN</strong>*: Initial dose one tablet daily. Adjust based on clinical response. Olmesartan and HCTZ have been used together in clinical trials in doses from 10 to 40 mg of olmesartan with 12.5 to 25 mg of HCTZ. Maximum dosage is one tablet of olmesartan/HCTZ 40 mg/25 mg per day.</td>
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<td>Agents</td>
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<td><strong>Byvalson</strong> (nebivolol/valsartan)</td>
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<td><strong>Cozaar</strong> (losartan)*</td>
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<td><strong>Diovan</strong> (valsartan)*</td>
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<td><strong>Diovan HCT</strong> (valsartan/HCTZ)*</td>
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<td><strong>Edarbi</strong> (azilsartan)</td>
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<td><strong>Edarbyclor</strong> (azilsartan/chorthalidone)</td>
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<td><strong>Exforge</strong> (valsartan/amldipine)*</td>
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<tr>
<td><strong>Exforge HCT</strong> (valsartan/amldipine/ HCTZ)*</td>
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<td><strong>Hyzaar</strong> (losartan/HCTZ)*</td>
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<td><strong>Micardis</strong> (telmisartan)*</td>
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<tr>
<td><strong>Micardis HCT</strong> (telmisartan/HCTZ)*</td>
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</table>
### Renin Inhibitors, Renin Inhibitor Combinations 18,19,24,25

<table>
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<tr>
<th>Agents</th>
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<th>CV Risk</th>
<th>HTN/LVH</th>
<th>Post-MI</th>
<th>HF</th>
<th>DMN</th>
</tr>
</thead>
</table>
| Amturnide  
(aliskiren/amlodipine/HCTZ) |     |         |         |         |    | Dosing and Administration (adults) |
| Tekamlo  
(aliskiren/amlodipine) |     |          |         |         |    | HTN: Initially, aliskiren 150mg/amlodipine 5 mg once daily. Titrate as needed up to maximum dose of 300 mg/10 mg daily. |
| Tekturina  
(aliskiren) |     |          |         |         |    | HTN: Initially, aliskiren 150 mg once daily. If BP remains uncontrolled, titrate up to 300 mg daily. Maximum dose- 300 mg/day. |
| Tekturina HCT  
(aliskiren/HCTZ) |     |          |         |         |    | HTN: Usual recommended starting dose is aliskiren/HCTZ 150/12.5 mg once daily. If BP remains uncontrolled after 2-4 weeks of therapy, may be titrated to a maximum of 300 mg aliskiren, 25 mg HCTZ. |

**Notes:**
- HTN = hypertension; LVH = left ventricular hypertrophy; MI = myocardial infarction; DMN = diabetic nephropathy;
- HCTZ = hydrochlorothiazide, HF=heart failure
- d- discontinued
CLINICAL RATIONALE
ACEIs & ARBs
Angiotensin Converting Enzyme Inhibitors (ACEIs) and Angiotensin II Receptor Blockers (ARBs) are recommended as a first-line pharmacotherapy options for patients with hypertension (HTN), HTN complicated by comorbidities, such as cerebrovascular disease, chronic kidney disease (of diabetic or nondiabetic origin), diabetes, heart failure (HF), left ventricular dysfunction and MI by national and international clinical guidelines and none of the guidelines have established a preference for one ACEI over another.23

ACC/AHA/AAPA/ABC/ACP/MAGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults (2017)36
- Thiazide diuretics, calcium channel blockers (CCBs), and ACEIs or ARBs are recommended as first line choices for initial antihypertensive drug therapy
- Adults with heart failure with preserved ejection fraction (HFpEF) and persistent HTN after management of volume overload should be prescribed ACEIs or ARBs and beta blockers titrated to attain SBP < 130 mmHg
- In adults with HTN and (Chronic Kidney Disease) CKD, ACEI treatment is reasonable to slow kidney disease progression
- For adults who experience a stroke or (transient ischemia attack) TIA, treatment with a thiazide diuretic, ACEI, or ARB, or combination treatment with thiazide/ACEI is useful
- In adults with Diabetes Mellitus (DM) and HTN, all first-line agents are useful and effective. ACEI and ARB therapy may be considered in the presence of albuminuria.
- Women with HTN who become pregnant should not be treated with ACEI, ARBs, or direct renin inhibitors

Clinical Practice Guidelines for screening and management of high blood pressure in children and adolescents from the American Academy of Pediatrics (2017)37
- Pharmacologic treatment of HTN in children and adolescents should be initiated in patients who have failed lifestyle modifications with an ACEI, ARB, long-acting CCB, or a thiazide diuretic.
  - Because African American children may not have as robust a response to ACEI treatment, it is recommended to consider a higher initial ACEI dose or use a thiazide diuretic or long-acting CCB.
  - In children with HTN and CKD, proteinuria, or diabetes mellitus, ACEI or ARB treatment is recommended as the initial antihypertensive agent unless there is an absolute contraindication

HTN with Coronary Artery Disease (CAD)31
- HF: Patients should be treated with ACE inhibitors (or ARBs), beta-blockers, and aldosterone receptor antagonists. Studies have shown equivalence of benefit of ACE inhibitors and the ARBs candesartan or valsartan in HF with reduced ejection fraction. Either class of agents is effective in lowering BP.
- Chronic stable angina: treatment regimen should include an ACE inhibitor or ARB if there is prior MI, LV systolic dysfunction, diabetes mellitus, or CKD.
- ACS: An ACE inhibitor or an ARB should be added if the patients has anterior MI, if HTN persists, if the patients has evidence of LV dysfunction or HF, or if the patient has diabetes mellitus.

2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults-Report from the Panel Members of the Eighth Joint National Committee (JNC8)23
- For the general nonblack population ≥60 years old (goal BP < 150/90) initial drug treatment options include thiazide-type diuretics, ACEIs, ARBs, or CCB.
- For diabetic patients (goal of BP <140/90) initial drug therapy includes thiazide type diuretics, ACEIs, ARBs, or CCBs.
• For patients with chronic kidney disease (CKD) [goal of BP <140/90], initial therapy options are ACEIs and ARBs.
• Because the majority of CKD patients with HTN will require > 1 drug to achieve goal BP, it is anticipated that an ACEI or ARB will be used as either initial therapy or as second-line therapy in addition to a diuretic or CCB in black patients with CKD.23

2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction (MI)27
An ACEI should be administered within the first 24 hours to all patients with STEMI with anterior location, HF, or EF ≤ 0.40, unless contraindicated (an alternative is an ARB).

2014 AHA/ACC Guideline for the Management of Patients with Non-ST Elevation Acute Coronary Syndrome38
• ARBs are recommended in patients with HF or MI with LVEF less than 0.40 who are ACE inhibitor intolerant.
• ARBs are reasonable in other patients with cardiac or other vascular disease who are ACE inhibitor intolerant

The 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation (AF)34
• ACEI or ARB treatment is reasonable for primary prevention of new-onset AF in patients with HFrEF.
• ACEI or ARB treatment may be considered for primary prevention of new-onset AF in the setting of hypertension

2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure33
• Inhibition of the renin-angiotensin system with ACEIs or ARBs or ARNI in conjunction with evidence-based beta blockers and aldosterone antagonists in selected patients is recommended for patients with chronic heart failure with reduced ejection fraction (HFrEF) to reduce morbidity and mortality.
• The use of ARBs to reduce morbidity and mortality is recommended in patients with prior or current symptoms of chronic HFrEF who are intolerant to ACEIs because of cough or angioedema
• The use of ARBs might be considered to decrease hospitalizations for patients with heart failure with preserved ejection fraction (HFP EF)

Diabetes and Kidney Disease

ACEIs
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.31

The Standards of Medical Care in Diabetes 2018 from the American Diabetes Association (ADA)29
• Treatment for hypertension should include drug classes demonstrated to reduce cardiovascular events in patients with diabetes (ACEIs, ARBs, thiazide-like diuretics, or dihydropyridine CCBs). Multiple-drug therapy is generally required to achieve blood pressure targets (but not a combination of ACEIs/ARBs).

The 2012 update of the Kidney Disease Outcomes Quality Initiative (KDOQI) Clinical Practice Guideline for Diabetes and Chronic Kidney Disease (CKD)30
“We suggest using an ACE-I or an ARB in normotensive patients with diabetes and albuminuria levels >30 mg/g who are at high risk of diabetic kidney disease or its progression.”

Safety
ACEIs and ARBs are contraindicated in pregnancy.

**Direct Renin Inhibitors**

The 2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults—Report from the Panel Members Appointed to the Eighth Joint National Committee (JNC 8) HTN guidelines note that direct renin inhibitors are not included in the current hypertension guideline recommendations because there were no studies demonstrating their benefits on kidney or CV outcomes. The current ADA and KDOQI guidelines do not provide any recommendations around the use of these medications in the treatment of hypertension in patients with diabetes and/or CKD.

The FDA added a new contraindication against the use of aliskiren with ARBs or ACEIs in patients with diabetes because of the risk of renal impairment, hypotension, and hyperkalemia. A warning was added to avoid use of aliskiren with ARBs or ACEIs in patients with moderate to severe renal impairment (i.e., where glomerular filtration rate [GFR] < 60 mL/min). The FDA stated that Valturna (a combination containing aliskiren and valsartan) should not be used in patients with diabetes and Valturna was removed from the market in July 2012.

**REFERENCES**

26. FDA. *FDA Drug Safety Communication: New Warning and Contraindication for blood pressure medicines containing aliskiren (Tekturna)*
Angiotensin II Receptor Antagonists (ARBs), Renin Inhibitors, and Combinations Step Therapy (1-Step)

OBJECTIVE
The intent of the Angiotensin II Receptor Antagonists (ARBs), Renin Inhibitors and Combinations Step Therapy (ST) program is to encourage use of cost-effective generic products - ACEIs, ACEI combinations (ACEI/diuretics or ACEI/calcium channel blockers [CCBs]), ARBs, or ARB combinations - over the more expensive brand ARBs, brand ARB combinations, brand renin inhibitors and renin inhibitor combinations (renin inhibitor/diuretic, renin inhibitor/ARB, or renin inhibitor/CCB). This program will accommodate for use of brand products when generic prerequisites cannot be used due to previous trial and failure, documented intolerance, FDA labeled contraindication, or hypersensitivity. Requests for brand ARB or renin inhibitor products will be reviewed when patient-specific documentation is provided.

TARGET AGENTS

| Angiotensin II Receptor Antagonists (ARBs), Combinations |
| Brand | Generic |
| Atacand® | candesartana |
| Atacand HCT® | candesartan/HCTZab |
| Avapro® | irbesartana |
| Avalide® | irbesartan/HCTZab |
| Azor® | olmesartan/amlodipinea |
| Benicar® | olmesartana |
| Benicar HCT® | olmesartan/HCTZab |
| Byvalson™ | nebivolol/valsartan |
| Cozaar® | losartana |
| Diovan® | valsartana |
| Diovan HCT® | valsartan/HCTZab |
| Edarbi® | azilsartan |
| Edarbyclor® | azilsartan/chlorthalidone |
| Eprosartan | eprosartan |
| Exforge® | valsartan/amlodipinea |
| Exforge HCT® | valsartan/amlodipine/HCTZab |
| Hyzaar® | losartan/HCTZab |
| Micardis® | telmisartana |
| Micardis HCT® | telmisartan/HCTZab |
| Teveten® | eprosartan |
| Teveten HCT® | eprosartan/HCTZb,c |
| Tribenzor® | olmesartan/amlodipine/HCTZa |
| Twynsta® | telmisartan/amlodipinea |

| Renin Inhibitors, Combinations |
| Brand | Generic |
| Amturnide® | aliskiren/amlodipine/HCTZb,c |
| Tekamlo® | aliskiren/amlodipinec |
| Tekturna® | aliskiren |
| Tekturna HCT® | aliskiren/HCTZb |

a – generic available that is a prerequisite agent for step therapy program
b - HCTZ = hydrochlorothiazide
c – discontinued
PRIOR AUTHORIZATION CRITERIA FOR APPROVAL

Brand ARBs, ARB Combinations, Renin Inhibitors, or Renin Inhibitor combinations will be approved when ONE of the following is met:

1. The patient’s medication history includes use of a generic ACEI, generic ACEI combination, generic ARB, or generic ARB combination product in the past 90 days

OR

2. There is documentation that the patient is currently using the requested brand ARB, ARB combination, renin inhibitor, or renin inhibitor combination, OR the requested brand ARB or renin inhibitor in another product (single ingredient or combination)

OR

3. The prescriber states the patient is using the requested brand ARB, ARB combination, renin inhibitor, or renin inhibitor combination or the requested brand ARB or renin inhibitor in another product (single ingredient or combination) AND is at risk if therapy is changed

OR

4. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to a generic ACEI, generic ACEI combination, generic ARB, or generic ARB combination product

Length of Approval: 12 months

NOTE: If Quantity Limit program also applies, please refer to Quantity Limit documents.
Step Therapy Supplement

This program applies to FlexRx Closed, FlexRx Open, GenRx Closed, GenRx Open, Health Insurance Marketplace, FocusRx and KeyRx formularies.

Please note, this does not include or apply to quantity limit questions.

STEP THERAPY SUPPLEMENT

OBJECTIVE

The intent of the Step Therapy Supplement is to provide additional questions, to ensure compliance to MN Statute 62Q.184. These questions will apply if the step therapy component within a Prior Authorization or Step Therapy program is not able to be approved.

CONDITIONS FOR APPROVAL

The requested agent will be approved when ONE of the following are met:

1. The patient is currently being treated with the requested agent as indicated by ALL of the following:
   a. A statement by the prescriber that the patient is currently taking the requested agent
      AND
   b. A statement by the prescriber that the patient is currently receiving a positive therapeutic outcome on requested agent
      AND
   c. The prescriber states that a change in therapy is expected to be ineffective or cause harm

   OR

2. The patient’s medication history include the required prerequisite/preferred agent(s) as indicated by:
   a. Evidence of a paid claim(s) within the past 999 days
      OR
   b. The prescriber has stated that the patient has tried the required prerequisite/preferred agent(s) in the past 999 days AND the required prerequisite/preferred agent(s) was discontinued due to lack of effectiveness or an adverse event

   OR

3. The prescriber has provided documentation that the required prerequisite/preferred agent(s) cannot be used due to a documented medical condition or comorbid condition that is likely to cause an adverse reaction, decrease ability of the patient to achieve or maintain reasonable functional ability in performing daily activities or cause physical or mental harm

Length of Approval: As per program specific criteria