Medical Policy

BlueCross BlueShield of Kansas
An independent licensee of the Blue Cross Blue Shield Association

Title: Antihypertensive Medications

- **Prime Therapeutics will review Prior Authorization requests**

Prior Authorization Form:
http://www.bcbsks.com/CustomerService/Forms/pdf/PriorAuth-6082KS-STQL.pdf

Link to Drug List (Formulary):
http://www.bcbsks.com/CustomerService/PrescriptionDrugs/drug_list.shtml

Professional
Original Effective Date: January 1, 2008
Revision Date(s): April 1, 2010; May 20, 2011; July 1, 2012; January 1, 2013; September 1, 2013; April 1, 2014; September 17, 2014; October 1, 2015; October 1, 2015; September 1, 2016; October 1, 2016; December 1, 2016
Current Effective Date: December 1, 2016

Institutional
Original Effective Date: January 1, 2008
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Current Effective Date: December 1, 2016

State and Federal mandates and health plan member contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. To verify a member's benefits, contact Blue Cross and Blue Shield of Kansas Customer Service.

The BCBSKS Medical Policies contained herein are for informational purposes and apply only to members who have health insurance through BCBSKS or who are covered by a self-insured group plan administered by BCBSKS. Medical Policy for FEP members is subject to FEP medical policy which may differ from BCBSKS Medical Policy.

The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents of Blue Cross and Blue Shield of Kansas and are solely responsible for diagnosis, treatment and medical advice.

If your patient is covered under a different Blue Cross and Blue Shield plan, please refer to the Medical Policies of that plan.

DESCRIPTION

The intent of the Antihypertensive Medication Prior Authorization 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 Drugs

Angiotensin II Receptor Antagonists (ARBs), Combinations	
Brand	**Generic**
Atacand®	candesartan[a]
Atacand HCT®	candesartan/HCTZ[ab]
Avalide®	irbesartan/HCTZ[ab]
Avapro®	irbesartan[a]
Azor®	olmesartan/amlodipine[a]
Benicar®	olmesartan[a]
Benicar HCT®	olmesartan/HCTZ[ab]
Byvalson™	nebivolol/valsartan
Cozaar®	losartan[a]
Diovan®	valsartan[a]
Diovan HCT®	valsartan/HCTZ[ab]
Edarbi®	azilsartan
Edarbyclor®	azilsartan/chlorthalidone
eprosartan	eprosartan
Exforge®	valsartan/amlodipine [a]
Exforge HCT®	valsartan/amlodipine/HCTZ[ab]
Hyzaar®	losartan/HCTZ[ab]
Micardis®	telmisartan[a]
Micardis HCT®	telmisartan/HCTZ[ab]
Teveten®	eprosartan
Teveten HCT®	eprosartan/HCTZ[b]
Tribenzor®	olmesartan/amlodipine/HCTZ[a]
Twynsta®	telmisartan/amlodipine[a]
Renin Inhibitors, Combinations	
Brand	**Generic**
Amturnide®	aliskiren/amlodipine/HCTZ[b]
Tekamlo®	aliskiren/amlodipine
Tekturna®	aliskiren
Tekturna HCT®	aliskiren/HCTZ[b]

a - generic available that is a prerequisite agent for step therapy program

b - HCTZ = hydrochlorothiazide

FDA Approved Indications and Dosage

ARBs and ARB Combinations[1-18,21-23,38]

Agents	HTN	CV Risk ↓	HTN / LVH	Post-MI	HF	DMN	Dosing and Administration (adults)
Atacand (candesartan)*	✓				✓ b d e		**HTN:** 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. **HF:** Initial, 4 mg once daily. Target dose, 32 mg once daily.
Atacand HCT (candesartan/HCTZ)*	✓						**HTN****: 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.
Avalide (irbesartan/HCTZ)*	✓						**HTN**: Initiate 150/12.5 mg once daily; titrate to 300/12.5 mg, then to a maximum of 300/25 mg once daily if needed.
Avapro (irbesartan)*	✓					✓ c	**HTN:** 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. **DMN:** Initially 75 mg/day. Target dose is 300 mg/day. There are no data on clinical effects of lower doses in DMN.
Azor (olmesartan/ amlodipine)*	✓						**HTN:** Initiate amlodipine/olmesartan 5/20 mg once daily (1 to 2 weeks), titrate to maximum of 10/40 mg once daily.
Benicar (olmesartan) *	✓						**HTN:** 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 >40 mg/day do not appear to have greater benefit; twice daily dosing has no advantage over the same dose given once daily.
Benicar HCT (olmesartan/HCTZ) *	✓						**HTN****: 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.
Byvalson (nebivolol/valsartan)	✓						**HTN:** 5 mg / 80 mg once daily
Cozaar (losartan)*	✓		✓ a			✓ c	**HTN:** Initial dose 50 mg once daily; 25 mg if volume depletion or hepatic impairment. May dose once or twice daily; total daily dose range is 25-100 mg. **HTN/LVH:** Usual initial dose is 50 mg once daily, may be increased to 100 mg once daily, followed by an increase in HCTZ to 25 mg once daily, based on BP response. **DMN:** Usual initial dose is 50 mg once daily. Dose should be increased to 100 mg once daily based on BP response.
Diovan (valsartan)*	✓			✓	✓ b d		**HTN:** Initially, 80 or 160 mg once daily in patients not volume depleted. Patients requiring greater reduction can start at the higher dose. Range 80-320 mg once daily. **Post-MI:** Initiate 20 mg twice daily as early as 12 hours after MI, titrate over 7 days up to 40 mg twice daily. Titrate to maintenance dose of 160 mg twice daily, as tolerated. **HF:** Initially, 40 mg twice daily. Titrate to highest dose tolerated, range of 80-160 mg twice daily (maximum dose).
Diovan HCT (valsartan/HCTZ)*	✓						**HTN:** Initiate with valsartan/HCTZ 160/12.5 mg once daily. Titrate to maximum of 320/25 mg once daily.

Agents	HTN	CV Risk ↓	HTN/ LVH	Post-MI	HF	DMN	Dosing and Administration (adults)
Edarbi (azilsartan)	✓						**HTN:** The recommended dose is 80 mg once daily. Consider starting dose of 40 mg in patients on high dose diuretics.
Edarbyclor (azilsartan/ chorthalidone)	✓						**HTN:** The recommended dose is 40/12.5 mg once daily. Maximum dose is 40/25 mg once daily.
Exforge (valsartan/ amlodipine)*	✓						**HTN:** When used as initial therapy, start with amlodipine/ valsartan 5/160 mg once daily; then titrate upwards as necessary to maximum of 10/320 mg once daily.
Exforge HCT (valsartan/ amlodipine/ HCTZ)*	✓						**HTN******:** Individualize the dosage by titration of amlodipine, HCTZ, and valsartan. The dosage of one or all components may be increased after 2 weeks. Maximum daily dose is 10 mg amlodipine, 25 mg HCTZ, and 320 mg valsartan.
Hyzaar (losartan/HCTZ)*	✓		✓ a				**HTN******:** Initial dose losartan/HCTZ 50/12.5 mg once daily. May increase to 2 tablets of 50/12.5 once daily or 1 tablet of 100/25 once daily. Max daily dose is losartan/HCTZ 100/25. **HTN/LVH:** Initially, 50 mg losartan once daily. May add HCTZ 12.5 mg once daily, may increase losartan to 100 mg, or use losartan/HCTZ 100/12.5 once daily. Maximum daily dosage is losartan/HCTZ 100/25.
Micardis (telmisartan)*	✓	✓					**HTN:** Usual initial dose is 40 mg once daily; 20 mg once daily if volume-depleted; range 20-80 mg once daily. **CV risk ↓:** Recommended dose 80 mg once daily; unknown if doses <80 mg are effective in reduction of cardiac morbidity and mortality.
Micardis HCT (telmisartan/HCTZ)*	✓						**HTN******:** Telmisartan/ HCTZ studied in clinical trials in doses 20-160 mg of telmisartan with HCTZ 6.25-25 mg. Maximum dose is two telmisartan/ HCTZ 80/12.5 mg tablets per day (160 mg/day telmisartan and 25 mg/day HCTZ).
Teveten, eprosartan	✓						**HTN:** Initially, 600 mg once daily in patients not volume depleted. Give once or twice daily, total daily doses range 400-800 mg. Limited experience with doses >800 mg/day.
Teveten HCT (eprosartan/HCTZ)	✓						**HTN******:** Initial dose is one tablet of eprosartan/ HCTZ 600/12.5 mg once daily, which may be increased to one tablet of eprosartan/HCTZ 600/25 mg once daily. If needed, an additional 200-300 mg eprosartan may be given. Eprosartan and HCTZ have been studied together in clinical trials in doses of 600-800 mg/day eprosartan (as single or divided doses) combined with 12.5-25 mg/day HCTZ. Maximum dosage - 900 mg/day eprosartan and 25 mg/day HCTZ.
Tribenzor (olmesartan/ amlodipine/HCTZ)*	✓						**HTN:** Dose once daily. Dosage may be increased after 2 weeks. The maximum recommended dose is 40/10/25 mg.
Twynsta (telmisartan/ amlodipine)*	✓						**HTN:** Initial: 1 tablet amlodipine/telmisartan 5/40 mg once daily. Initiate with amlodipine/ telmisartan 5/80 mg once daily in patients requiring larger BP reductions. Maximum dose: 10 mg/day amlodipine/80 mg/day telmisartan.

HTN=hypertension; LVH=left ventricular hypertrophy; MI=myocardial infarction; DMN=diabetic nephropathy; HCTZ=hydrochlorothiazide, HF=heart failure; CV risk ↓=cardiovascular risk reduction (MI, stroke, death) in high risk patients unable to take ACE inhibitors

All ACEI and ARB single entity agents may be used as monotherapy or in combination for the treatment of hypertension.

*agents available as generics

**To minimize dose independent side effects, it is usual to begin combination therapy only after patients fail to achieve desired effects with monotherapy; combination products may be substituted for previously titrated components.

a - Reduction in the risk of stroke in patients with hypertension and LVH

b - Treatment of heart failure [New York Heart Association (NYHA) class II-IV] in patients unable to tolerate an ACEI

c - Treatment of DMN with an elevated serum creatinine and in patients with type 2 diabetes and HTN

d - In patients intolerant of ACEIs e - In combination with ACEI

Renin Inhibitors, Renin Inhibitor Combinations[19,20,26,27]

Agents	HTN	CV Risk ↓	HTN/LVH	Post-MI	HF	DMN	Dosing and Administration (adults)
Amturnide (aliskiren/ amlodipine/HCTZ)	✓						**HTN:** Initial dosing will depend on prior therapy. Dose once-daily. Titrate as needed up to maximum dose- of 300 mg/10 mg/25 mg once daily.
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.
Tekturna (aliskiren)	✓						**HTN:** Initially, aliskiren 150 mg once daily. If BP remains uncontrolled, titrate up to 300 mg daily. Maximum dose - 300 mg/day.
Tekturna 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.

HTN=hypertension; LVH=left ventricular hypertrophy; MI=myocardial infarction; DMN=diabetic nephropathy; HCTZ=hydrochlorothiazide, HF=heart failure

POLICY

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 or generic ARB combination product.

Length of Approval: 12 months

RATIONALE

Hypertension

ACEIs & ARBs

ACEIs and 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, 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.[24,25]

HTN with Coronary Artery Disease (CAD)[37]

- 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):[24]

- 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.[24]

2013 ESH/ESC Guidelines for themanagement of arterial HTN:[25]

- For the general nonelderly (goal of <140/90) initial treatment recommended are beta blockers, diuretic, CCBs, ACEIs, ARBs, and CCBs.
- For diabetic patients (goal of <140/85) initial treatment should be with an ACEI or ARB.
- CKD patients with no proteinuria, ACEIs and ARBs are recommended as initial treatment.

2013 American College of Cardiology Foundation (ACCF)/American Heart Association Guideline for the Management of HF:[30]

ACEIs are recommended in patients with HF and reduced ejection fraction (EF) and current or prior symptoms, unless contraindicated, to reduce morbidity and mortality (with the highest level of recommendation). The available data suggest that there are no differences among ACEIs in their effects on symptoms or survival.

2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction (MI) recommends the following:[31]
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).

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.[32]

The Standards of Medical Care in Diabetes 2015 from the American Diabetes Association (ADA) states:[33]
Pharmacological therapy for patients with diabetes and hypertension should comprise a regimen that includes either an ACE inhibitor or an angiotensin receptor blocker (ARB). If one class is not tolerated, the other should be substituted.

The 2012 update of the Kidney Disease Outcomes Quality Initiative (KDOQI) Clinical Practice Guideline for Diabetes and Chronic Kidney Disease (CKD) state:[34]
"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. Their use in the second half of pregnancy has been associated with oligohydramnios and neonatal anuria, growth abnormalities, skull hypoplasia and fetal death. The agents in this class contain a boxed warning in their labeling to warn of this problem.[35] The American College of Obstetricians and Gynecologists (ACOG) 2013 Guidelines-HTN in Pregnancy state:[35] For women with uncomplicated chronic HTN in pregnancy, the use of and ACEI or ARB are not recommended. For women of reproductive age with chronic HTN, the use of ACEIs and ARBs is not recommended unless there is a compelling reason such as the presence of proteinuric renal disease.[35] The most common adverse effects of ACEIs are hypotension (which occurs early in treatment in about 20% if of patients) and dizziness.[35]

An increase in serum creatinine (e.g., 0.3 mg/dL) with the use of ACEIs is observed in 15%-30% of patients with severe HF, but in only 5%-15% of patients with mild to moderate symptoms. The risks are substantially greater if the patient has renal artery stenosis.[36] Cough related to ACEIs is the most common reason for the withdrawal of long term treatment with these drugs. The frequency is approximately 5%-10% of white patients and up to 50% in Chinese patients.[36]

If the cough proves to be persistent and troublesome the physician should consider withdrawal of the ACEI and use an alternative medication such as an ARB.[36]

The American College of Cardiology/ American Heart Association HF guidelines state "With the use of ACEIs, particular care should be given to patient's volume status, renal function, and concomitant medications, however most HF patients (85% to 90%) can tolerate these drugs."[30]

Direct Renin Inhibitors
Aliskiren was evaluated by the FDA for treatment of hypertension in a large clinical development program including five primary randomized, double-blind, placebo-controlled studies (these are all

published); several other supportive studies (posters/abstracts and/or unpublished) were reviewed by the FDA as well. The five pivotal studies were randomized, double-blind, placebo-controlled, 8 week trials, with a primary endpoint of change from baseline in seated trough cuff diastolic blood pressure (DBP). Some trials evaluated active control arms, and/or combinations with another antihypertensive. The FDA felt that these studies provided evidence that aliskiren reduces blood pressure (BP). Blood pressure reduction was typically seen after two weeks of therapy, and effects were maximal by four weeks. Antihypertensive effects were sustained for at least 11 months in a randomized, double-blind, placebo controlled withdrawal at the end of a long-term safety study.[19,20]

In January 2012, Novartis Pharmaceuticals sent out a safety letter informing healthcare professionals of the results of the Aliskiren Trial in Type 2 Diabetics Using Cardio-Renal Endpoints (ALTITUDE) trial.[28] The ALTITUDE study was conducted in type 2 diabetic patients, known to be at risk of fatal and non-fatal cardiovascular and renal events. In this study, aliskiren 300 mg (or placebo) was given in addition to standard of care, including an angiotensin ACEI or an ARB. The independent Data Monitoring Committee overseeing the trial concluded that patients were unlikely to benefit from treatment added to standard antihypertensives. The committee also noted a higher adverse event rate in these high-risk patients receiving aliskiren combined with standard care. Specifically, the committee highlighted an increased incidence of nonfatal stroke, renal complications, hyperkalemia and hypotension among those who had received 18 to 24 months of treatment with aliskiren as well as standard therapy.

As a result of the ALTITUDE study, 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)[19,29]. 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.[29]

REVISIONS

05-20-2011	Revision
07-01-2012	Revision
01-01-2013	Revision
09-01-2013	Revision
04-01-2014	Policy posted July 15, 2014.
	Administrative Update
	In Description section: ▪ In the Target Drugs chart noted generic availability that is a prerequisite agent for step therapy program on Micardis (telmisartan) and Twynsta (telmisartan / amlodipine) ▪ In ARBs and ARB Combinations chart noted generic availability of Avalide (irbesartan / HCTZ) and Avapro (irbesartan).
	References updated
09-17-2014	Description section ▪ Target Drugs and FDA Approved Indications and Dosage charts revised to remove Valturna (aliskiren/valsartan).
	In Policy section:

	▪ In Item A 3 removed "prescribing physician" and added "provider" to read, "The prescriber states the patient…"
	Rationale section updated
	In Coding section ▪ HCPCS Codes confirmed
	References updated
10-01-2015	Policy published 11-10-2015. Administrative Update retro-effective to 10-01-2015.
	Description section updated to include the addition of "eprosartan" to the Target Drugs and updates to the FDA Approved Indications and Dosage chart.
	Rationale section updated
	Removed Coding section
	References updated
10-01-2015	Policy published 12-22-2015. Updates retro-effective to 10-01-2015.
	Description section updated to include updates to the FDA Approved Indications and Dosage chart.
	References updated
09-01-2016	Description section updated
	In Policy section ▪ In Item 1 added "in the past 90 days" to read "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"
	Rationale section updated
	Revision section updated to remove details of the 05-20-2011, 07-01-2012, 01-01-2013, and 09-01-2013 updates.
	References updated
10-01-2016	Policy published 10-12-2016. Policy retro-effective to 10-01-2016.
	In Description section: ▪ Added Byvalson nebivolol/valsartan to the Target Drug and FDA Approved Indications and Dosage chart.
	References updated
12-01-2016	Policy published 12-29-2016. Policy retro-effective to 12-01-2016.
	In Description section: ▪ Updated Target Drugs chart and FDA Indications and Dosage chart noting generic availability of Azor, Benicar, Benicar/HCTZ, and Tribenzor.

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