Medical Policy

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

Title: Neprilysin Inhibitor (Entresto™)

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

  Prior Authorization Form:
  http://www.bcbsks.com/CustomerService/Forms/pdf/PriorAuth-6375KS-NEPR.pdf

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

Professional
Original Effective Date: July 12, 2015
Revision Date(s): July 12, 2015, January 1, 2016; January 1, 2017
Current Effective Date: January 1, 2017

Institutional
Original Effective Date: July 12, 2015
Revision Date(s): July 12, 2015, January 1, 2016; January 1, 2017
Current Effective Date: January 1, 2017

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.

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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 Neprilysin Inhibitor prior authorization (PA) and Quantity Limit (QL) program is to appropriately select patients for therapy according to product labeling and/or clinical guidelines and according to dosing recommended in product labeling. Neprilysin inhibitors will be approved for use in patients with New York Heart Association (NYHA) Stage II-IV chronic heart failure, who have a reduced baseline or current ejection fraction ≤40%; and patients who are on a beta blocker or who have a documented intolerance, FDA labeled contraindication, or hypersensitivity to a beta blocker. The program will not allow approval for patients who have an FDA labeled contraindication to the requested agent, or for patients who are pregnant, or for patients who will use the requested agent concomitantly with another ACEI or ARB. The program will approve for doses within the set limit. Doses above the set limit will be approved if the requested quantity is below the FDA limit and cannot be dose optimized or when the quantity is above the FDA limit and the prescriber has submitted documentation in support of therapy with a higher dose for the intended diagnosis. Requests will be reviewed when patient specific documentation is provided.

Target Drug

- **Entresto**™ (sacubitril/valsartan)

FDA Approved Indications and Dosage[1]

	Indication	Dosage & Administration
Entresto™ (sacubitril/valsartan)	Reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure (NYHA Class II-IV) and reduced ejection fraction. Sacubitril/valsartan is usually administered in conjunction with other heart failure therapies, in place of an ACE inhibitor or other ARB.	The recommended starting dose of sacubitril/valsartan is 49/51 mg twice-daily. Double the dose of sacubitril/valsartan after 2 to 4 weeks to the target maintenance dose of 97/103 mg twice-daily, as tolerated by the patient. Reduce the starting dose to 24/26 mg twice-daily for: • Patients not currently taking an ACEi or an ARB or previously taking a low dose of these agents • Patients with severe renal impairment • Patients with moderate hepatic impairment Double the dose of sacubitril/valsartan every 2 to 4 weeks to the target maintenance dose of 97/103 mg twice-daily, as tolerated by the patient.

POLICY

Prior Authorization and Quantity Limit Criteria for Approval

Neprilysin Inhibitor will be approved when ALL of the following are met:

1. The patient has a diagnosis of chronic heart failure NYHA Class II, III, or IV
   AND
2. The patient has a baseline OR current left ventricular ejection fraction of ≤40%
   AND
3. ONE of the following:
   a. The patient is currently taking a beta blocker (e.g. atenolol, bisoprolol, carvedilol, metoprolol)
      OR
   b. The patient has a history of a documented intolerance, FDA labeled contraindication, or hypersensitivity to a beta blocker
   AND
4. ONE of the following:
   a. The patient is not currently taking another ACE Inhibitor or ARB
      OR
   b. The patient will discontinue the other current ACE Inhibitor or ARB before starting the requested agent
   AND
5. The patient does NOT have any FDA labeled contraindication(s) to the requested agent
   AND
6. The patient is NOT pregnant
   AND
7. ONE Of the following:
   a. The requested quantity (dose) is NOT greater than the program quantity limit
      OR
   b. ALL of the following:
      i. The requested quantity (dose) is greater than the program quantity limit
         AND
      ii. The requested quantity (dose) is less than or equal to the FDA labeled dose
         AND
      iii. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the limit
      OR

c. ALL of the following:
   i. The requested quantity (dose) is greater than the program quantity limit **AND**
   ii. The requested quantity (dose) is greater than the FDA labeled dose **AND**
   iii. The prescriber has submitted documentation in support of therapy with a higher dose for the intended diagnosis (must be reviewed by the Clinical Review pharmacist)

Length of Approval: 12 months

Brand (generic)	Quantity Limit Per Day
Entresto (sacubitril/valsartan)	
24/26 mg tablets	2 tablets
49/51 mg tablets	2 tablets
97/103 mg tablets	2 tablets

Agent	Contraindication(s)
Entresto (sacubitril/valsartan)	▪ Hypersensitivity to any component. ▪ History of angioedema related to previous ACEi or ARB therapy. ▪ Concomitant use with ACEi. ▪ Concomitant use with aliskiren in patients with diabetes.

RATIONALE

Guidelines[2]

Sacubitril/valsartan was approved after the current 2013 American College of Cardiology Foundation (ACCF) and American Heart Association (AHA) Practice Guideline for the Management of Heart Failure was published. The guideline does not currently include sacubitril/valsartan.

The ACCF/AHA guideline classifies heart failure by the following in relation to New York Heart Association (NYHA) Functional Classification:

ACCF/AHA Stages of HF	ACCF/AHA Stage Description	NYHA Functional Classification	NYHA Functional Classification Description
A	At high risk for HF but without structural heart disease or symptoms of HF	None	None
B	Structural heart disease but without signs or symptoms of HF	I	No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF

ACCF/AHA Stages of HF	ACCF/AHA Stage Description	NYHA Functional Classification	NYHA Functional Classification Description
C	Structural heart disease with prior or current symptoms of HF	I	No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF
		II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in symptoms of HF
		III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes symptoms of HF
		IV	Unable to carry on any physical activity without symptoms of HF, or symptoms of HF at rest
D	Refractory HF requiring specialized interventions	IV	Unable to carry on any physical activity without symptoms of HF, or symptoms of HF at rest

The ACCF/AHA guideline recommends the following algorithm for the treatment of heart failure with reduced ejection fraction (≤40%) ACCF/AHA Class C and NYHA Class I-IV:

- All patients should receive an angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) in addition to a beta blocker
- For volume overloaded NYHA Class II-IV patients, a loop diuretic should be added
- For persistently symptomatic African American NYHA class III-IV patients, hydralazine and isosorbide dinitrate should be added
- For NYHA Class II-IV patients with estimated creatinine >30 mL/min and potassium <5.0 mEq/dL, an aldosterone antagonist should be added

ACC/AHA/HFSA recommends an angiotensin receptor/neprilysin inhibitor (ARNI) combination, as an alternative to ACEI or ARB, in conjunction with evidence-based beta blockers, and aldosterone antagonists in select patients with chronic Heart Failure with reduced Ejection Fraction (HFrEF) to reduce morbidity and mortality. ACC/AHA/HFSA also states that in patients with chronic symptomatic HFrEF NYHA class II or III who tolerate an ACEI or ARB, replacement by an ARNI is recommended to further reduce morbidity and mortality.[3]

Efficacy[1]

Sacubitril/valsartan was studied in PARADIGM-HF, a multinational, randomized, double-blind trial comparing sacubitril/valsartan and enalapril in 8,442 adult patients with symptomatic chronic heart failure (NYHA class II–IV) and systolic dysfunction (left ventricular ejection fraction ≤ 40%). Patients had to have been on an ACE inhibitor or ARB for at least four weeks and on maximally tolerated doses of beta-blockers. Patients with a systolic blood pressure of < 100 mmHg at screening were excluded. The primary objective of PARADIGM-HF was to determine whether sacubitril/valsartan, a combination of sacubitril and a RAS inhibitor (valsartan), was superior to a RAS inhibitor (enalapril) alone in reducing the risk of the combined endpoint of cardiovascular (CV) death or hospitalization for heart failure (HF). After discontinuing their existing ACE inhibitor or ARB therapy, patients entered sequential single-blind run-in periods during which they received enalapril 10 mg twice-daily, followed by sacubitril/valsartan 100 mg twice-daily, increasing to 200 mg twice daily. Patients who successfully completed the sequential

run-in periods were randomized to receive either sacubitril/valsartan 200 mg (N=4,209) twice-daily or enalapril 10 mg (N=4,233) twice-daily. The primary endpoint was the first event in the composite of CV death or hospitalization for HF. The median follow-up duration was 27 months and patients were treated for up to 4.3 years.

The mean left ventricular ejection fraction was 29%. The underlying cause of heart failure was coronary artery disease in 60% of patients; 71% had a history of hypertension, 43% had a history of myocardial infarction, 37% had an eGFR < 60 mL/min/1.73m2 , and 35% had diabetes mellitus. Most patients were taking beta-blockers (94%), mineralocorticoid antagonists (58%), and diuretics (82%). Few patients had an implantable cardioverter-defibrillator (ICD) or cardiac resynchronization therapy-defibrillator (CRT-D) (15%).

PARADIGM-HF demonstrated that sacubitril/valsartan, was superior to enalapril, in reducing the risk of the combined endpoint of cardiovascular death or hospitalization for heart failure, based on a time-to-event analysis (hazard ratio [HR]: 0.80, 95% confidence interval [CI], 0.73, 0.87, p=0.0001). The treatment effect reflected a reduction in both cardiovascular death and heart failure hospitalization. Sudden death accounted for 45% of cardiovascular deaths, followed by pump failure, which accounted for 26%. Sacubitril/valsartan also improved overall survival (HR 0.84; 95% CI [0.76, 0.93], p = 0.0009). This finding was driven entirely by a lower incidence of cardiovascular mortality on sacubitril/valsartan.

Safety[1]

During the sacubitril/valsartan run-in period, an additional 10.4% of patients permanently discontinued treatment, 5.9% because of an adverse event, most commonly renal dysfunction (1.8%), hypotension (1.7%) and hyperkalemia (1.3%). Because of this run-in design, the adverse reaction rates described below are lower than expected in practice. In the double-blind period, safety was evaluated in 4,203 patients treated with sacubitril/valsartan and 4,229 treated with enalapril. In PARADIGM-HF, patients randomized to sacubitril/valsartan received treatment for up to 4.3 years, with a median duration of exposure of 24 months; 3,271 patients were treated for more than one year. Discontinuation of therapy because of an adverse event during the double-blind period occurred in 450 (10.7%) of sacubitril/valsartan treated patients and 516 (12.2%) of patients receiving enalapril. Adverse reactions occurring at an incidence of ≥5% in patients who were treated with sacubitril/valsartan in the double-blind period are shown below:

In the PARADIGM-HF trial, the incidence of angioedema was 0.1% in both the enalapril and sacubitril/valsartan run-in periods. In the double-blind period, the incidence of angioedema was higher in patients treated with sacubitril/valsartan than enalapril (0.5% and 0.2%, respectively). The incidence of angioedema in Black patients was 2.4% with sacubitril/valsartan and 0.5% with enalapril. Orthostasis was reported in 2.1% of patients treated with sacubitril/valsartan compared to 1.1% of patients treated with enalapril during the double-blind period of PARADIGM-HF. Falls were reported in 1.9% of patients treated with sacubitril/valsartan compared to 1.3% of patients treated with enalapril.

Table 1. Adverse Reactions Reported in ≥5% of Patients Treated with Sacubitril/Valsartan in the Double-Blind Period

	Sacubitril/Valsartan (n=4,203) %	Enalapril (n=4,229) %
Hypotension	18	12
Hyperkalemia	12	14
Cough	9	13
Dizziness	6	5
Renal failure/acute renal failure	5	5

Sacubitril/valsartan carries a black box warning that drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus and when pregnancy is detected, sacubitril/valsartan should be discontinued as soon as possible.

REVISIONS

07-12-2015	Entresto (sacubitril / valsartan) added to New to Market Drug medical policy (effective 07-12-2015)
01-01-2016	New Stand alone policy published 12-22-2015. Policy effective 01-01-2016.
	Added specific drug prior authorization criteria and quantity limits.
01-01-2017	Published 12-20-2016. Effective 01-01-2017.
	Description section updated
	▪ In Policy section: ▪ In Item 1 added "chronic" to read "The patient has a diagnosis of chronic heart failure NYHA Class II, III, or IV" Added Item 4 "ONE of the following: a. The patient is not currently taking another ACE Inhibitor or ARB OR b. The patient will discontinue the other current ACE Inhibitor or ARB before starting the requested agent"
	Rationale section updated
	References updated

REFERENCES

1. Entresto prescribing information. Novartis Pharmaceuticals Inc. July 2015.
2. 2013 ACCF/AHA Guideline for the Management of Heart Failure. Accessed on 5/23/2016. http://circ.ahajournals.org/
3. 2016 ACC/AHA/HFSA Focused Update on New Pharmacological Therapy for Heart Failure: An Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure. A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America Developed in Collaboration With the International Society of Heart and Lung Transplantation. Accessed on 5/23/2016. http://circ.ahajournals.org/