Entresto® (sacubitril/valsartan)

NOTICE

This policy contains information which is clinical in nature. The policy is not medical advice. The information in this policy is used by Wellmark to make determinations whether medical treatment is covered under the terms of a Wellmark member's health benefit plan. Physicians and other health care providers are responsible for medical advice and treatment. If you have specific health care needs, you should consult an appropriate health care professional. If you would like to request an accessible version of this document, please contact customer service at 800-524-9242.

BENEFIT APPLICATION

Benefit determinations are based on the applicable contract language in effect at the time the services were rendered. Exclusions, limitations or exceptions may apply. Benefits may vary based on contract, and individual member benefits must be verified. Wellmark determines medical necessity only if the benefit exists and no contract exclusions are applicable. This policy may not apply to FEP. Benefits are determined by the Federal Employee Program.

DESCRIPTION

The intent of the Entresto® (sacubitril/valsartan) drug policy is to ensure appropriate selection of patients for therapy based on product labeling, clinical guidelines and clinical studies. This combination agent combines sacubitril, a neprilysin inhibitor, with the angiotensin II receptor blocker (ARB) valsartan to form a single agent. It is a first-in-class angiotensin II-receptor neprilysin inhibitor (ARNI).

FDA-Approved Indications

1. Reduce the risk of cardiovascular death and hospitalization for heart failure in adult patients with chronic heart failure (NYHA Class II-IV) and reduced ejection fraction.
2. Treatment of symptomatic HF with systemic left ventricular systolic dysfunction in pediatric patients ≥1 year of age.

POLICY

Criteria for Initial Approval

I. Entresto (sacubitril/valsartan) may be considered **medically necessary** for the treatment of NYHA class II, III, or IV heart failure with an ejection fraction of less than or equal to 40% when the following criteria is met:
   - Patient must be 18 years of age or older
   - Must be prescribed by, or in consultation with, a cardiologist
   - Patient will continue to concomitantly receive a maximally tolerated dose of a beta blocker unless contraindicated or is currently receiving a beta blocker and plan to titrate to maximally tolerated dose

- The patient does NOT have any of the following: a history of angioedema, concomitant use of ACE inhibitors or ARBs, concomitant use of aliskiren in a patient with diabetes, pregnancy, or hypotension.

Approval will be for **12 months**

II. Entresto (sacubitril/valsartan) may be considered **medically necessary** for the treatment of symptomatic heart failure with systemic left ventricular systolic dysfunction when the following criteria is met:
- Patient must be greater than or equal to 1 year of age and less than 18 years of age
- Must be prescribed by, or in consultation with, a cardiologist
- The patient does NOT have any of the following: a history of angioedema, concomitant use of ACE inhibitors or ARBs, concomitant use of aliskiren in a patient with diabetes, pregnancy, or hypotension.

Approval will be for **12 months**

Continuation of Therapy

I. The continuation of Entresto (sacubitril/valsartan) may be considered **medically necessary** for the treatment of NYHA class II, III, or IV heart failure with an ejection fraction of less than or equal to 40% when the following criteria is met:
- Patient has had a documented clinical response to Entresto therapy and is tolerating treatment
- Patient is currently receiving maximum pharmaceutical therapy for heart failure including a maximally tolerated dose of a beta blocker unless contraindicated

Approval will be for **36 months**

II. The continuation of Entresto (sacubitril/valsartan) may be considered **medically necessary** for the treatment of symptomatic heart failure with systemic left ventricular systolic dysfunction when the following criteria is met:
- Patient must be greater than or equal to 1 year of age
- Patient has had a documented clinical response to Entresto therapy and is tolerating treatment

Approval will be for **36 months**

Entresto (sacubatril/valsartan) is considered **not medically necessary** for patients who do not meet the criteria set forth above.

Dosing and Administration

Approvals may be subject to dosing limits in accordance with FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines.

Quantity Limit

Entresto 60 tablets/30days

CLINICAL RATIONALE

Adult Use

Entresto is indicated to 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. The Prospective comparison of Angiotensin Receptor neprilysin inhibitors with Angiotensin converting enzyme inhibitors to

Determine Impact on Global Mortality and morbidity in Heart Failure (PARADIGM-HF) was a multinational, randomized, double-blind trial in patients with symptomatic chronic heart failure (NYHA class II to IV) and systolic dysfunction (left ventricular EF ≤ 40% - later changed to ≤ 35%) stabilized on an ACEI or ARB for at least four weeks and on maximally tolerated doses of β-blockers (N=8,442). After discontinuing their existing ACEI/ARB therapy, patients entered sequential single-blind run-in periods during which they received enalapril 10 mg twice-daily for two weeks then held therapy with enalapril for one day, followed by sacubitril/valsartan 100 mg twice-daily, increasing to 200 mg twice daily for four to six weeks. Following these run-in periods, the sacubitril/valsartan was also held for one day prior to patients being randomized to sacubitril/valsartan 200 mg twice-daily or enalapril 10 mg twice daily. The primary endpoint was the first event in the composite of cardiovascular death or hospitalization for HF.

Sacubitril/valsartan was associated with a greater risk reduction for the primary endpoint of composite of death from cardiovascular causes or hospitalization for heart failure compared to enalapril (914 patients [21.8%] vs 1,117 patients [26.5%]; hazard ratio [HR], 0.80; 95% confidence interval [CI], 0.73 to 0.87; P <0.0001). The treatment effect reflected a reduction in cardiovascular death (558 patients in the sacubitril/valsartan group [13.3%] and 693 patients in the enalapril group [16.5%]) and HF hospitalization (537 patients in the sacubitril/valsartan group [12.8%] vs 658 patients in the enalapril group [15.6%]). In addition, sacubitril/valsartan was associated with a reduction in all-cause mortality compared to enalapril (711 [17.0%] vs 835 [19.8%]; HR, 0.84; 95% CI, 0.76 to 0.93; P <0.0001). The study was stopped early when a highly statistically significant reduction in the risk of cardiovascular death was achieved in the sacubitril/valsartan group.

The 2017 American College of Cardiology/American Heart Association/Heart Failure Society of America Focused Heart Failure update included a Class I recommendation that an ACE inhibitor, ARB, or ARNI may be utilized for patients with chronic HFrEF to reduce morbidity and mortality. ACE inhbitors and ARBs have a high quality level of evidence, while Entresto is rated as having moderate quality evidence.

The PARAGON-HF (Prospective Comparison of ARNI with ARB Global Outcomes in HF with Preserved Ejection Fraction) trial compared Entresto (sacubitril–valsartan) with valsartan alone in patients with heart failure with preserved ejection fraction. The trial included 4822 patients who were 50 years of age or older with New York Heart Association (NYHA) class II to IV heart failure, ejection fraction of 45% or higher, elevated level of natriuretic peptides, and structural heart disease to receive sacubitril–valsartan (target dose, 97 mg of sacubitril with 103 mg of valsartan twice daily) or valsartan (target dose, 160 mg twice daily). The primary outcome was a composite of total hospitalizations for heart failure and death from cardiovascular causes. Primary outcome components, secondary outcomes (including NYHA class change, worsening renal function, and change in Kansas City Cardiomyopathy Questionnaire [KCCQ] clinical summary score [scale, 0 to 100, with higher scores indicating fewer symptoms and physical limitations]), and safety were also assessed. The patients (51% of whom were women) in 43 countries underwent randomization after a single-blind run-in period.

After a median of 35 months, there were 894 primary events (hospitalizations for heart failure and deaths from cardiovascular causes) in the sacubitril–valsartan group and 1009 primary events in the valsartan group (rate ratio, 0.87; 95% confidence interval [CI], 0.75 to 1.01; P=0.06). The incidence of death from cardiovascular causes was 8.5% in the sacubitril–valsartan group and 8.9% in the valsartan group (hazard ratio, 0.95; 95% CI, 0.79 to 1.16). There were 690 hospitalizations for heart failure in the sacubitril–valsartan group and 797 in the valsartan group (rate ratio, 0.85; 95% CI, 0.72 to 1.00). The mean change in the KCCQ clinical summary score at 8 months was 1.0 point (95% CI, 0.0 to 2.1) higher in the sacubitril–valsartan group. Patients in the sacubitril–valsartan group had a higher incidence of hypotension and angioedema and a lower incidence of hyperkalemia. Among 12 prespecified subgroups, there was suggestion of heterogeneity with possible benefit with sacubitril–valsartan in patients with lower ejection fraction and in women. Overall, Entresto did not result in a significantly lower rate of total hospitalizations for heart failure and death from cardiovascular causes among patients with heart failure with preserved

ejection fraction. The study did identify some signals suggestive of benefit, despite a neutral result for the primary end point, which investigators concluded that further research is required to determine the role of Entresto in patients with heart failure and ejection fraction that is below normal but not frankly reduced.

Pediatric Use

The efficacy of Entresto was evaluated in a multinational, randomized, double-blind trial comparing Entresto and enalapril based on an analysis in 110 pediatric patients 1 to <18 years old with heart failure (NYHA/Ross class II-IV) due to systemic left ventricular systolic dysfunction (LVEF ≤40%). Patients with systemic right ventricles and single ventricles were excluded from the trial. The target maintenance dose of Entresto in pediatric patients 1 to <18 years old was 3.1 mg/kg twice daily.

The endpoint was the between-group difference in the change in plasma NT-proBNP from baseline to 12 weeks. The reduction from baseline in NT-proBNP was 44% and 33% in the Entresto and enalapril groups, respectively. While the between-group difference was not statistically significant, the reductions for Entresto and enalapril were similar to or larger than what was seen in adults; these reductions did not appear to be attributable to post-baseline changes in background therapy. Because Entresto improved outcomes and reduced NT-proBNP in PARADIGM-HF, the effect on NT-proBNP was considered a reasonable basis to infer improved cardiovascular outcomes in pediatric patients.

Safety and effectiveness have not been established in pediatric patients less than 1 year of age.

Additional Information

Entresto is contraindicated in patients with a history of angioedema related to previous ACE inhibitor or ARB therapy; with concomitant use of ACE inhibitors, and with concomitant use of aliskiren in patients with diabetes. Do not administer within 36 hours of switching from or to an ACE inhibitor. Also, avoid use of Entresto with an ARB.

The prescribing information states that Entresto can cause fetal harm when administered to a pregnant woman. Furthermore, a boxed warning states that when pregnancy is detected Entresto should be discontinued as soon as possible.

Entresto is available as tablets, containing sacubitril 24 mg/valsartan 26 mg; sacubitril 49 mg /valsartan 51 mg; and sacubitril 97 mg /valsartan 103 mg. The recommended starting dose of Entresto is 49 mg/51 mg twice-daily. The prescriber should double the dose of Entresto after 2 weeks to 4 weeks to the target maintenance dose of 97 mg/103 mg twice daily, as tolerated by the patient.

PROCEDURES AND BILLING CODES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD Diagnostic Codes.

- No applicable codes

REFERENCES

- Entresto [package insert]. East Hanover, New Jersey: Novartis Pharmaceuticals Corporation; October 2019.
- McMurray JV, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med*. 2014;371(11):993-1004.
- Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur. Heart J.* 2016;37:2129-2200.

- Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure. Journal of the American College of Cardiology. 2017;70(6).
- Shaddy R, Canter C, Halnon N, et al. Design for the sacubitril/valsartan (LCZ696) compared with enalapril study of pediatric patients with heart failure due to systemic left ventricle systolic dysfunction (PANORAMA-HF study). Am Heart J. 2017;193:23-34.
- Solomon SD, McMurray JJV, Anand IS, et al. Angiotensin–neprilysin inhibition in heart failure with preserved ejection fraction. N Engl J Med 2019;381:1609-1620.

POLICY HISTORY

Policy #: 05.01.87
Policy Creation: November 2015
Reviewed: April 2020
Revised: January 2020
Current Effective Date: February 24, 2020