Entresto® (sacubitril/valsartan)

**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).

Entresto® is approved by the Food and Drug Administration (FDA) 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.

**POLICY**

I. Initiation of Entresto® (sacubitril/valsartan) may be considered medically necessary for the treatment of NYHA class II, III, or IV heart failure symptoms 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
   - The patient has been stabilized on an angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) for at least four weeks prior to initiation of therapy
   - Patient is and will continue to concomitantly receive a maximally tolerated dose of a beta blocker unless contraindicated
   - The patient does NOT have any of the following: a history of angioedema related to previous ACE inhibitor or ARB therapy; concomitant use of ACE inhibitors or ARBs; concomitant use of aliskiren in a patient with diabetes; pregnancy; baseline systolic blood pressure less than or equal to 100 mmHg

Approval will be for 12 months

II. The continuation of Entresto® (sacubitril/valsartan) may be considered medically necessary for the treatment of NYHA class II, III, or IV heart failure symptoms 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 12 months

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

Quantity limits apply: Entresto 60 tablets/30 days

CLINICAL RATIONALE

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 2016 European Society of Cardiology Heart Failure Guidelines and 2016 American College of Cardiology/American Heart Association/Heart Failure Society of America Focused Heart Failure update both include Entresto as a Class I recommendation for use in reduced ejection fraction heart failure patients in place of ACEI or ARB therapy. Level of evidence for each guideline is B due to moderate rather than high quality evidence. Entresto is to be used in patients previously tolerating an ACEI or ARB and is recommended to further reduce morbidity and mortality in conjunction with other standard of care therapies.

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**


**POLICY HISTORY**

Policy #: 05.01.87
Policy Creation: November 2015
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