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. Benefits are most clearly evident in patients with left ventricular ejection fraction (LVEF) below normal.
2. Treatment of symptomatic HF with systemic left ventricular systolic dysfunction in pediatric patients ≥1 year of age. Entresto reduces NT-proBNP and is expected to improve cardiovascular outcomes.

POLICY

Criteria for Approval

I. Entresto (sacubitril/valsartan) may be considered **medically necessary** for the treatment of heart failure when the following criteria is met:
   - Patient must be 18 years of age or older
   - The requested drug is being prescribed to reduce the risk of cardiovascular death and hospitalization for heart failure
   - The patient meets ONE of the following:

1. The patient has a diagnosis of symptomatic chronic heart failure with a baseline or current left ventricular ejection fraction (LVEF) of less than or equal to 40 percent. Documentation is required for approval.

   AND

   The patient will receive concomitant treatment with a maximally tolerated dose of a beta-blocker (e.g., carvedilol, metoprolol succinate, bisoprolol) or the patient has experienced an intolerance to a beta-blocker (e.g., carvedilol, metoprolol succinate, bisoprolol) or the patient has a contraindication that would prohibit a trial of a beta-blocker (e.g., carvedilol, metoprolol succinate, bisoprolol)

OR

2. The patient has structural heart disease (i.e., left atrial enlargement [LAE], left ventricular hypertrophy [LVH]). Documentation is required for approval.

- If the patient has a diagnosis of diabetes, the requested drug will not be used in combination with Tekturna (aliskiren)
- If the patient has renal impairment (estimated Glomerular Filtration Rate [eGFR] less than 60 milliliters per minute per 1.73 meters squared [mL/min/1.73m2]), the requested drug will not be used in combination with Tekturna (aliskiren)

Approval will be for **36 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 1 year of age or older
   - The requested drug is being prescribed for the treatment of symptomatic heart failure with systemic left ventricular systolic dysfunction
   - If the patient has a diagnosis of diabetes, the requested drug will not be used in combination with Tekturna (aliskiren)
   - If the patient has renal impairment (estimated Glomerular Filtration Rate [eGFR] less than 60 milliliters per minute per 1.73 meters squared [mL/min/1.73m2]), the requested drug will not be used in combination with Tekturna (aliskiren)

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

The intent of the criteria is to provide coverage consistent with product labeling, FDA guidance, standards of medical practice, evidence-based drug information, and/or published guidelines. Entresto (sacubitril and valsartan) is a combination of a neprilysin inhibitor and an angiotensin II receptor blocker (ARB). Entresto is indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in adult patients

with chronic heart failure. Benefits are most clearly evident in patients with left ventricular ejection fraction (LVEF) below normal. LVEF is a variable measure, so use clinical judgment in deciding whom to treat. Entresto is also indicated for the treatment of symptomatic heart failure with systemic left ventricular systolic dysfunction in pediatric patients aged one year and older.

The concomitant use of Entresto with Tekturna (aliskiren) is contraindicated in patients with diabetes. In addition, concomitant use of Entresto with Tekturna should be avoided in patients with renal impairment (eGFR < 60 mL/min/1.73m2). Therefore, Entresto will not be approved if the patient meets any of these conditions.

Adult Use

PARADIGM-HF was a multinational, randomized, double-blind trial comparing Entresto 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 angiotensin-converting enzyme inhibitor (ACEI) or ARB for at least four weeks and on maximally tolerated doses of beta-blockers. Therefore, patients with systolic dysfunction (left ventricular ejection fraction ≤ 40%) must have a diagnosis of symptomatic chronic heart failure in order to receive approval.

The 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure expanded guideline-directed medical therapy (GDMT) to include four classes: 1) renin-angiotensin system inhibition (RASi) with angiotensin receptor-neprilysin inhibitors (ARNi), angiotensin-converting enzyme inhibitors (ACEi), or angiotensin (II) receptor blockers (ARB) alone; 2) beta blockers (carvedilol, metoprolol succinate, or bisoprolol); 3) mineralocorticoid receptor antagonists (MRA); and 4) sodium-glucose cotransporter-2 inhibitors (SGLT2i). ARNi is now recommended as first-line RASi to reduce morbidity and mortality in HFrEF (Class of Recommendation 1a). ACEi is recommended when ARNi is not feasible, and ARB in those who are ACEi intolerant and when ARNi is not feasible. In symptomatic patients with HFrEF who tolerate ACEi or ARB, replacement with ARNi is recommended for further reduction in morbidity and mortality. Beta-blocker doses should be adjusted every 2 weeks in a patient with no evidence of decompensated heart failure and no contraindications to higher doses until a maximally tolerated or target dose is achieved. Due to clinical trial requirements and guideline recommendations, patients with systolic dysfunction (left ventricular ejection fraction ≤ 40%) must also receive concomitant treatment with a maximally tolerated dose of a beta-blocker, or they must have experienced an intolerance or contraindication to beta-blocker use in order to receive approval.

The 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure also recommends that GDMT be continued in patients with previous HFrEF who have a LVEF over 40% (now classified as HF with improved EF [HFimpEF]), including those who are asymptomatic, to prevent relapse of HF and LV dysfunction. Resolution of symptoms and improvement in cardiac function and biomarkers after treatment reflects remission only which requires treatment to be maintained, even in patients with previous HFrEF who may become asymptomatic.

PARAGON-HF was a multicenter, randomized, double-blind trial comparing Entresto and valsartan in 4,796 adult patients with symptomatic heart failure with left ventricular ejection fraction ≥45%, and structural heart disease [either left atrial enlargement (LAE) or left ventricular hypertrophy (LVH)]. Patients with any prior echocardiographic LVEF <40% at screening were excluded. The American College of Cardiology Foundation/American Heart Association (ACCF/AHA) 2013 heart failure guidelines state that heart failure with preserved ejection fraction (HFpEF) has been variably classified as ejection fraction >40%, >45%, >50% and ≥55%. Therefore, patients with a LVEF greater than 40% and no previous LVEF less than 40% must have a diagnosis of symptomatic chronic heart failure and have structural heart disease (i.e., left atrial enlargement [LAE], left ventricular hypertrophy [LVH]) in order to receive approval. An LVEF greater than 40% was chosen in order to include all HFpEF ejection fraction classifications per the 2013 guidelines and

to account for patients who do not meet the defined HFrEF criteria of a left ventricular ejection fraction ≤ 40%.

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.

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

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POLICY HISTORY

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