PRIOR AUTHORIZATION CRITERIA

BRAND NAME*
(generic)

ENTRESTO
(sacubitril and valsartan)

Status: CVS Caremark Criteria ***Ref # 1277-A***
Type: Initial Prior Authorization ***Ref # 1276-A***

** Drugs that are listed in the target drug box include both brand and generic and all dosage forms and strengths unless otherwise stated. OTC products are not included unless otherwise stated.*

FDA-APPROVED INDICATIONS

Adult Heart Failure
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.

Pediatric Heart Failure
Entresto is indicated for the treatment of symptomatic heart failure with systemic left ventricular systolic dysfunction in pediatric patients aged one year and older. Entresto reduces NT-proBNP and is expected to improve cardiovascular outcomes.

COVERAGE CRITERIA

The requested drug will be covered with prior authorization when the following criteria are met:

- The patient is 18 years of age or older
  AND
- The requested drug is being prescribed to reduce the risk of cardiovascular death and hospitalization for heart failure
  AND
- The patient has a diagnosis of symptomatic chronic heart failure
  AND
  - The patient has any of the following: A) left ventricular ejection fraction less than or equal to 40 percent (i.e., Heart Failure with reduced Ejection Fraction [HFrEF]), B) previous left ventricular ejection fraction less than or equal to 40 percent and a follow-up left ventricular ejection fraction measurement of greater than 40 percent (i.e., Heart Failure with improved Ejection Fraction [HFimpEF]). The prescriber MUST submit chart notes or other documentation supporting a current or previous left ventricular ejection fraction percentage less than or equal to 40 percent.
    AND
  - Chart notes or other documentation supporting a current or previous left ventricular ejection fraction of less than or equal to 40 percent have been submitted to CVS Health
    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

- The patient has any of the following: A) left ventricular ejection fraction of 41 to 49 percent (i.e., Heart Failure with mildly reduced Ejection Fraction [HFmrEF]), B) left ventricular ejection fraction greater than or equal to 50 percent (i.e., Heart Failure with preserved Ejection Fraction [HFpEF])
  AND
- The patient has evidence or history of spontaneous or provokable increased left ventricular filling pressures (e.g., elevated natriuretic peptide, noninvasive and invasive hemodynamic measurement). The prescriber MUST submit chart notes or other documentation supporting evidence or history of spontaneous or provokable increased left ventricular filling pressures.
  AND
- Chart notes or other documentation supporting evidence or history of spontaneous or provokable increased left ventricular filling pressures have been submitted to CVS Health

OR

- This request is for a pediatric patient one year of age or older
  AND
- The requested drug is being prescribed for the treatment of symptomatic heart failure with systemic left ventricular systolic dysfunction

AND

- If the patient has a diagnosis of diabetes, the requested drug will not be used in combination with Tekturna (aliskiren)
  OR
- If the patient has renal impairment (estimated Glomerular Filtration Rate [eGFR] less than 60 milliliters per minute per 1.73 meters squared [mL/min/1.73m^2]), the requested drug will not be used in combination with Tekturna (aliskiren)

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.[1,3]

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%). 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)].[1] Therefore, patients must have a diagnosis of symptomatic chronic heart failure in order to receive approval.

According to the 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure, left ventricular ejection fraction (LVEF) is considered important in the classification of patients with heart failure (HF) because of differing prognosis and response to treatments. In this guideline, heart failure with reduced ejection fraction (HFrEF) is defined as LVEF ≤ 40%. Heart failure with improved ejection fraction (HFimpEF) is used to characterize patients with HF who had a previous LVEF ≤ 40% and a follow-up measurement of LVEF > 40%. Although associated with better outcomes, improvement in LVEF does not mean full myocardial recovery or normalization of LV function. In most patients, cardiac structural abnormalities, such as LV chamber dysfunction, may persist. Furthermore, changes in LVEF might not be unidirectional; a patient may have improvement followed by a decrease in EF or vice versa depending on the underlying cause, duration of disease, adherence to guideline-directed medical therapy (GDMT) or reexposure to cardiac toxicity. Importantly, EF can decrease

after withdrawal of pharmacological treatments in many patients who had improved EF to normal range with GDMT.[4] Therefore, in patients with HFimpEF after treatment, GDMT should be continued to prevent relapse of HF and left ventricular (LV) dysfunction, even in patients who become asymptomatic.

Angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), angiotensin receptor-neprilysin inhibitors (ARNI) and beta-blockers are considered part of GDMT for HFrEF.[4] In the PARADIGM-HF trial, 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.[1] Therefore, patients with HFrEF and HFimpEF must also receive concomitant treatment with a maximally tolerated dose of a beta-blocker, or they must have experienced an intolerance or have a contraindication to beta-blocker use.

The 2022 AHA/ACC/HFSA Guideline defines the threshold for heart failure with preserved ejection fraction (HFpEF) as an LVEF ≥ 50%. Patients with HF and an LVEF between the HFrEF and HFpEF range (41% to 49%) have been termed as heart failure with mildly reduced ejection fraction (HFmrEF). The diagnosis of HFmrEF and HFpEF can be challenging. Although the classic clinical signs and symptoms of HF, together with EF of 41% to 49% or ≥ 50%, respectively, are necessary for the diagnosis of HFmrEF and HFpEF, the requirements for additional measures of cardiac dysfunction can improve the diagnostic specificity. The signs and symptoms of HF are frequently nonspecific and overlap with other clinical conditions. To improve the specificity of diagnosis of HFmrEF and HFpEF, the clinical diagnosis of HF in these EF categories should be further supported by objective measures. For this reason, the guideline-writing committee proposes the addition of evidence of spontaneous (at rest) or provokable (e.g., during exercise, fluid challenge) increased LV filling pressures (e.g., elevated natriuretic peptide, noninvasive/invasive hemodynamic measurement) to the classifications of HFmrEF and HFpEF.[4] Therefore, requests for patients with HFmrEF and HFpEF will require evidence or history of spontaneous or provokable increased LV filling pressures.

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/1.73m^2).[1] Therefore, Entresto will not be approved if the patient meets any of these conditions.

REFERENCES

1. Entresto [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; February 2021.
2. Lexicomp Online, AHFS DI (Adult and Pediatric) Online, Hudson, Ohio: UpToDate, Inc.; 2022; Accessed June 20, 2022.
3. Micromedex (electronic version). IBM Watson Health, Greenwood Village, Colorado, USA. Available at: https://www.micromedexsolutions.com. Accessed June 20, 2022.
4. Heidenreich PA, Bozkurt B, Aguilar D et. al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol.* 2022; 79:e263-e421.

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Reviewed:	Medical Affairs: (KU) 07/2015; (LS) 03/2017; (CHART) 11/27/2019, 3/26/2020, 04/21/2022, 07/28/2022 External Review: 08/2015, 06/2016, 06/2017, 06/2018, 06/2019, 12/2019 (FYI), 06/2020, 06/2021, 06/2022, 10/2022

CRITERIA FOR APPROVAL

1	Is the patient 18 years of age or older? [If no, then skip to question 12.]	Yes	No

2	Is the requested drug being prescribed to reduce the risk of cardiovascular death and hospitalization for heart failure? [If no, then no further questions.]	Yes	No
3	Does the patient have a diagnosis of symptomatic chronic heart failure? [If no, then no further questions.]	Yes	No
4	Does the patient have any of the following: A) left ventricular ejection fraction less than or equal to 40 percent (i.e., Heart Failure with reduced Ejection Fraction [HFrEF]), B) previous left ventricular ejection fraction less than or equal to 40 percent and a follow-up left ventricular ejection fraction measurement of greater than 40 percent (i.e., Heart Failure with improved Ejection Fraction [HFimpEF])? [If yes, then prescriber MUST submit chart notes or other documentation supporting a current or previous left ventricular ejection fraction percentage less than or equal to 40 percent.] [Tech Note: Leave as answered by prescriber. Verification of chart note will be addressed in question 5.] [If no, then skip to question 9.]	Yes	No
5	Have chart notes or other documentation supporting a current or previous left ventricular ejection fraction of less than or equal to 40 percent been submitted to CVS Health? [Tech Note: MUST obtain a physical copy of chart notes or other documentation supporting evidence of current or previous left ventricular ejection fraction of less than or equal to 40 percent. If the PA is worked over the phone, then the prescriber still MUST submit physical chart notes or other documentation. If a physical copy of documentation of evidence of current or previous left ventricular ejection fraction less than or equal to 40 percent is not received, then the PA should be denied.] [If no, then no further questions.]	Yes	No
6	Will the patient receive concomitant treatment with a maximally tolerated dose of a beta-blocker (e.g., carvedilol, metoprolol succinate, bisoprolol)? [If yes, then skip to question 14.]	Yes	No
7	Has the patient experienced an intolerance to a beta-blocker (e.g., carvedilol, metoprolol succinate, bisoprolol)? [If yes, then skip to question 14.]	Yes	No
8	Does the patient have a contraindication that would prohibit a trial of a beta-blocker (e.g., carvedilol, metoprolol succinate, bisoprolol)? [If yes, then skip to question 14.] [If no, then no further questions.]	Yes	No
9	Does the patient have any of the following: A) left ventricular ejection fraction of 41 to 49 percent (i.e., Heart Failure with mildly reduced Ejection Fraction [HFmrEF]), B) left ventricular ejection fraction greater than or equal to 50 percent (i.e., Heart Failure with preserved Ejection Fraction [HFpEF])? [If no, then no further questions.]	Yes	No

10	Does the patient have evidence or history of spontaneous or provokable increased left ventricular filling pressures (e.g., elevated natriuretic peptide, noninvasive and invasive hemodynamic measurement)? [If yes, then prescriber MUST submit chart notes or other documentation supporting evidence or history of spontaneous or provokable increased left ventricular filling pressures.] [Tech Note: Leave as answered by prescriber. Verification of chart note will be addressed in question 11.] [If no, then no further questions.]	Yes	No
11	Have chart notes or other documentation supporting evidence or history of spontaneous or provokable increased left ventricular filling pressures been submitted to CVS Health? [Tech Note: MUST obtain a physical copy of chart notes or other documentation supporting evidence or history of spontaneous or provokable increased left ventricular filling pressures. If the PA is worked over the phone, then the prescriber still MUST submit physical chart notes or other documentation. If a physical copy of documentation of evidence or history of spontaneous or provokable increased left ventricular filling pressures is not received, then the PA should be denied.] [If yes, then skip to question 14.] [If no, then no further questions.]	Yes	No
12	Is this request for a pediatric patient one year of age or older? [If no, then no further questions.]	Yes	No
13	Is the requested drug being prescribed for the treatment of symptomatic heart failure with systemic left ventricular systolic dysfunction? [If no, then no further questions.]	Yes	No
14	Does the patient have a diagnosis of diabetes? [If yes, then skip to question 16.]	Yes	No
15	Does the patient have renal impairment (estimated Glomerular Filtration Rate [eGFR] less than 60 milliliters per minute per 1.73 meters squared [mL/min/1.73m2])? [If no, then no further questions.]	Yes	No
16	Will the requested drug be used in combination with Tekturna (aliskiren)?	Yes	No

Mapping Instructions 1276-A			
	Yes	**No**	**DENIAL REASONS – DO NOT USE FOR MEDICARE PART D**
1.	Go to 2	Go to 12	
2.	Go to 3	Deny	You do not meet the requirements of your plan. Your plan covers this drug when you are using it to reduce your risk of death and being hospitalized for heart failure. Your request has been denied based on the information we have. [Short Description: No approved use-adult]

3.	Go to 4	Deny	You do not meet the requirements of your plan. Your plan covers this drug when you have a diagnosis of symptomatic chronic heart failure. Your request has been denied based on the information we have. [Short Description: No approvable diagnosis-adult]
4.	Go to 5	Go to 9	
5.	Go to 6	Deny	You do not meet the requirements of your plan. Your plan covers this drug when your prescriber submits chart notes or other documentation to CVS Health that supports that you have or had a left ventricular ejection fraction percentage less than or equal to 40 percent. Your request has been denied based on the information we have. [Short Description: Prescriber did not submit documentation of current or previous LVEF less than or equal to 40 percent]
6.	Go to 14	Go to 7	
7.	Go to 14	Go to 8	
8.	Go to 14	Deny	You do not meet the requirements of your plan. Your plan covers this drug when you are taking a beta-blocker, or you cannot use it. Your request has been denied based on the information we have. [Short Description: No intolerance, contraindication, or use of maximally tolerated beta-blocker]
9.	Go to 10	Deny	You do not meet the requirements of your plan. Your plan covers this drug when you meet any of these conditions: - You have an ejection fraction less than or equal to 40 percent - You had an ejection fraction less than or equal to 40 percent, but it has improved - You have an ejection fraction between 41 and 49 percent - You have an ejection fraction greater than or equal to 50 percent Your request has been denied based on the information we have. [Short Description: No appropriate LVEF measurement for approval]
10.	Go to 11	Deny	You do not meet the requirements of your plan. Your plan covers this drug when you have evidence or history of spontaneous or provokable increased left ventricular filling pressures. Your request has been denied based on the information we have. [Short Description: No evidence or history of increased LV filling pressures]
11.	Go to 14	Deny	You do not meet the requirements of your plan. Your plan covers this drug when your prescriber submits chart notes or other documentation to CVS Health that supports evidence or history of spontaneous or provokable increased left ventricular filling pressures. Your request has been denied based on the information we have. [Short Description: Prescriber did not submit documentation of increased LV filling pressures]
12.	Go to 13	Deny	You do not meet the requirements of your plan. Your plan covers this drug when you are taking it for an approved use when you are one year of age or older. Your request has been denied based on the information we have. [Short Description: No approvable age]

13.	Go to 14	Deny	You do not meet the requirements of your plan. Your plan covers this drug when you have symptomatic heart failure with systemic left ventricular systolic dysfunction. Your request has been denied based on the information we have. [Short Description: No approvable diagnosis-pediatric]
14.	Go to 16	Go to 15	
15.	Go to 16	Approve, 12 months	
16.	Deny	Approve, 12 months	You do not meet the requirements of your plan. Your plan covers this drug when you meet all of these conditions: - You will not use it with Tekturna (aliskiren) if you have diabetes - You will not use it with Tekturna (aliskiren) if you have reduced renal function Your request has been denied based on the information we have. [Short Description: Concomitant use with Tekturna (aliskiren) and patient has diabetes or reduced renal function]

Mapping Instructions 1277-A			
	Yes	**No**	**DENIAL REASONS – DO NOT USE FOR MEDICARE PART D**
1.	Go to 2	Go to 12	
2.	Go to 3	Deny	You do not meet the requirements of your plan. Your plan covers this drug when you are using it to reduce your risk of death and being hospitalized for heart failure. Your request has been denied based on the information we have. [Short Description: No approved use-adult]
3.	Go to 4	Deny	You do not meet the requirements of your plan. Your plan covers this drug when you have a diagnosis of symptomatic chronic heart failure. Your request has been denied based on the information we have. [Short Description: No approvable diagnosis-adult]
4.	Go to 5	Go to 9	
5.	Go to 6	Deny	You do not meet the requirements of your plan. Your plan covers this drug when your prescriber submits chart notes or other documentation to CVS Health that supports that you have or had a left ventricular ejection fraction percentage less than or equal to 40 percent. Your request has been denied based on the information we have. [Short Description: Prescriber did not submit documentation of current or previous LVEF less than or equal to 40 percent]
6.	Go to 14	Go to 7	
7.	Go to 14	Go to 8	
8.	Go to 14	Deny	You do not meet the requirements of your plan. Your plan covers this drug when you are taking a beta-blocker, or you cannot use it. Your request has been denied based on the information we have. [Short Description: No intolerance, contraindication, or use of maximally tolerated beta-blocker]
9.	Go to 10	Deny	You do not meet the requirements of your plan. Your plan covers this drug when you meet any of these conditions: - You have an ejection fraction less than or equal to 40 percent - You had an ejection fraction less than or equal to 40 percent, but it has improved

			- You have an ejection fraction between 41 and 49 percent - You have an ejection fraction greater than or equal to 50 percent Your request has been denied based on the information we have. [Short Description: No appropriate LVEF measurement for approval]
10.	Go to 11	Deny	You do not meet the requirements of your plan. Your plan covers this drug when you have evidence or history of spontaneous or provokable increased left ventricular filling pressures. Your request has been denied based on the information we have. [Short Description: No evidence or history of increased LV filling pressures]
11.	Go to 14	Deny	You do not meet the requirements of your plan. Your plan covers this drug when your prescriber submits chart notes or other documentation to CVS Health that supports evidence or history of spontaneous or provokable increased left ventricular filling pressures. Your request has been denied based on the information we have. [Short Description: Prescriber did not submit documentation of increased LV filling pressures]
12.	Go to 13	Deny	You do not meet the requirements of your plan. Your plan covers this drug when you are taking it for an approved use when you are one year of age or older. Your request has been denied based on the information we have. [Short Description: No approvable age]
13.	Go to 14	Deny	You do not meet the requirements of your plan. Your plan covers this drug when you have symptomatic heart failure with systemic left ventricular systolic dysfunction. Your request has been denied based on the information we have. [Short Description: No approvable diagnosis-pediatric]
14.	Go to 16	Go to 15	
15.	Go to 16	Approve, 36 months	
16.	Deny	Approve, 36 months	You do not meet the requirements of your plan. Your plan covers this drug when you meet all of these conditions: - You will not use it with Tekturna (aliskiren) if you have diabetes - You will not use it with Tekturna (aliskiren) if you have reduced renal function Your request has been denied based on the information we have. [Short Description: Concomitant use with Tekturna (aliskiren) and patient has diabetes or reduced renal function]