

PRIOR AUTHORIZATION CRITERIA

BRAND NAME*
(generic)

ENTRESTO
(sacubitril and valsartan)

Status: CVS Caremark Criteria
Type: Initial Prior Authorization

Ref # 1277-A
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 a left ventricular ejection fraction (LVEF) 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**
- The patient has structural heart disease (i.e., left atrial enlargement [LAE], left ventricular hypertrophy [LVH]). Documentation is required for approval.
- 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/1.73m²]), 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}

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).¹ Therefore, Entresto will not be approved if the patient meets any of these conditions.

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.¹ 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 2021 update to the 2017 American College of Cardiology (ACC) expert consensus decision pathway for optimization of heart failure treatment can serve as interim guidance to clinicians during the comprehensive heart failure guideline update under development by the ACC. The 2021 update treatment algorithm for guideline-directed medical therapy including novel therapies in adults recommends an angiotensin receptor-neprilysin inhibitor (ARNI) (preferred), ACEI, or ARB, and an evidence-based beta-blocker (carvedilol, metoprolol succinate, or bisoprolol) with a diuretic agent, as needed, as the mainstay of therapy for heart failure with reduced ejection fraction (HFrEF). 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.⁴ 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.

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.¹ 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%.⁵ Therefore, patients with a LVEF greater 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%.

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.; 2021; Accessed February 23, 2021.
3. Micromedex (electronic version). Truven Health Analytics, Greenwood Village, Colorado, USA. <http://www.micromedexsolutions.com/>. Accessed February 23, 2021.
4. Maddox TM, Januzzi JL, Allen LA, et al. 2021 Update to the 2017 ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment: Answers to 10 Pivotal Issues About Heart Failure With Reduced Ejection Fraction: A Report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol*. Published online January 2021. Available at: https://www.jacc.org/doi/10.1016/j.jacc.2020.11.022?_ga=2.266943758.1073019511.1611765807-2024013049.1611765807
5. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA Guideline for the Management of Heart Failure. *J Am Coll Cardiol*. 2013;62(16):e147-e239.

Written by: UM Development (MS/SE)
Date Written: 07/2015
Revised: (LN) 08/2015 (added reduced ejection fraction); (MS) 03/2016 (no clinical changes), 03/2016 (editorial changes for readability), (MS) 03/2017; (ME) 03/2018 (no clinical changes); (KC) 03/2019 (no clinical changes), 11/2019 (added new indication); (CF) 03/2020 (no clinical changes); (CJH) 02/2021 (added new indication, updated coverage criteria)
Reviewed: Medical Affairs: (KU) 07/2015; (LS) 03/2017; (CHART) 11/27/2019, 3/26/2020, 3/4/2021
External Review: 08/2015, 06/2016, 06/2017, 06/2018, 06/2019, 12/2019 (FYI), 06/2020, 03/2020, 03/2021

CRITERIA FOR APPROVAL

- | | | | |
|---|---|-----|----|
| 1 | Is the patient 18 years of age or older?
[If no, then skip to question 9.] | 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 a left ventricular ejection fraction (LVEF) less than or equal to 40 percent?
[If yes, then documentation is required for approval.]

Left ventricular ejection fraction percentage _____

[If no, then skip to question 8.] | Yes | No |
| 5 | 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 11.] | Yes | No |
| 6 | Has the patient experienced an intolerance to a beta-blocker (e.g., carvedilol, metoprolol succinate, bisoprolol)?
[If yes, then skip to question 11.] | Yes | No |
| 7 | Does the patient have a contraindication that would prohibit a trial of a beta-blocker (e.g., | Yes | No |

	carvedilol, metoprolol succinate, bisoprolol)? [If yes, then skip to question 11.] [If no, then no further questions.]		
8	Does the patient have structural heart disease (i.e., left atrial enlargement [LAE], left ventricular hypertrophy [LVH])? [Note: If yes, then prescriber MUST submit chart notes or other documentation supporting a diagnosis of structural heart disease.] [If yes, then skip to question 11.] [If no, then no further questions.]	Yes	No
9	Is this request for a pediatric patient one year of age or older? [If no, then no further questions.]	Yes	No
10	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
11	Does the patient have a diagnosis of diabetes? [If yes, then skip to question 13.]	Yes	No
12	Does the patient have renal impairment (estimated Glomerular Filtration Rate [eGFR] less than 60 milliliters per minute per 1.73 meters squared [mL/min/1.73m ²])? [If no, then no further questions.]	Yes	No
13	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 9	
2.	Go to 3	Deny	You do not meet the requirements of your plan. Your plan covers this drug when you meet all of these conditions: - You are an adult - 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 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 8	
5.	Go to 11	Go to 6	
6.	Go to 11	Go to 7	
7.	Go to 11	Deny	You do not meet the requirements of your plan. Your plan covers this drug when you meet all of these conditions: - Your prescriber submits documentation that supports that you have an ejection fraction less than or equal to 40 percent

			- 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 with ejection fraction less than or equal to 40 percent]
8.	Go to 11	Deny	You do not meet the requirements of your plan. Your plan covers this drug when you meet all of these conditions: - You have an ejection fraction greater than 40 percent - Your prescriber submits documentation that supports that you have structural heart disease Your request has been denied based on the information we have. [Short Description: No documentation of structural heart disease with ejection fraction greater than 40 percent]
9.	Go to 10	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 approved age]
10.	Go to 11	Deny	You do not meet the requirements of your plan. Your plan covers this drug when you meet all of these conditions: - You are a pediatric patient one year of age or older - You have heart failure with left ventricular systolic dysfunction Your request has been denied based on the information we have. [Short Description: No approvable diagnosis-pediatric]
11.	Go to 13	Go to 12	
12.	Go to 13	Approve, 12 months	
13.	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 9	
2.	Go to 3	Deny	You do not meet the requirements of your plan. Your plan covers this drug when you meet all of these conditions: - You are an adult - 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 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 8	
5.	Go to 11	Go to 6	
6.	Go to 11	Go to 7	
7.	Go to 11	Deny	<p>You do not meet the requirements of your plan. Your plan covers this drug when you meet all of these conditions:</p> <ul style="list-style-type: none"> - Your prescriber submits documentation that supports that you have an ejection fraction less than or equal to 40 percent - You are taking a beta-blocker or you cannot use it <p>Your request has been denied based on the information we have.</p> <p>[Short Description: No intolerance, contraindication, or use of maximally tolerated beta-blocker with ejection fraction less than or equal to 40 percent]</p>
8.	Go to 11	Deny	<p>You do not meet the requirements of your plan. Your plan covers this drug when you meet all of these conditions:</p> <ul style="list-style-type: none"> - You have an ejection fraction greater than 40 percent - Your prescriber submits documentation that supports that you have structural heart disease <p>Your request has been denied based on the information we have.</p> <p>[Short Description: No documentation of structural heart disease with ejection fraction greater than 40 percent]</p>
9.	Go to 10	Deny	<p>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.</p> <p>[Short Description: No approved age]</p>
10.	Go to 11	Deny	<p>You do not meet the requirements of your plan. Your plan covers this drug when you meet all of these conditions:</p> <ul style="list-style-type: none"> - You are a pediatric patient one year of age or older - You have heart failure with left ventricular systolic dysfunction <p>Your request has been denied based on the information we have.</p> <p>[Short Description: No approvable diagnosis-pediatric]</p>
11.	Go to 13	Go to 12	
12.	Go to 13	Approve, 36 months	
13.	Deny	Approve, 36 months	<p>You do not meet the requirements of your plan. Your plan covers this drug when you meet all of these conditions:</p> <ul style="list-style-type: none"> - 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 <p>Your request has been denied based on the information we have.</p> <p>[Short Description: Concomitant use with Tekturna (aliskiren) and patient has diabetes or reduced renal function]</p>